

# Respiratory Threats in the Tropics

## WRAIR-GEIS Operational Infectious Disease Course

**WRAIR**

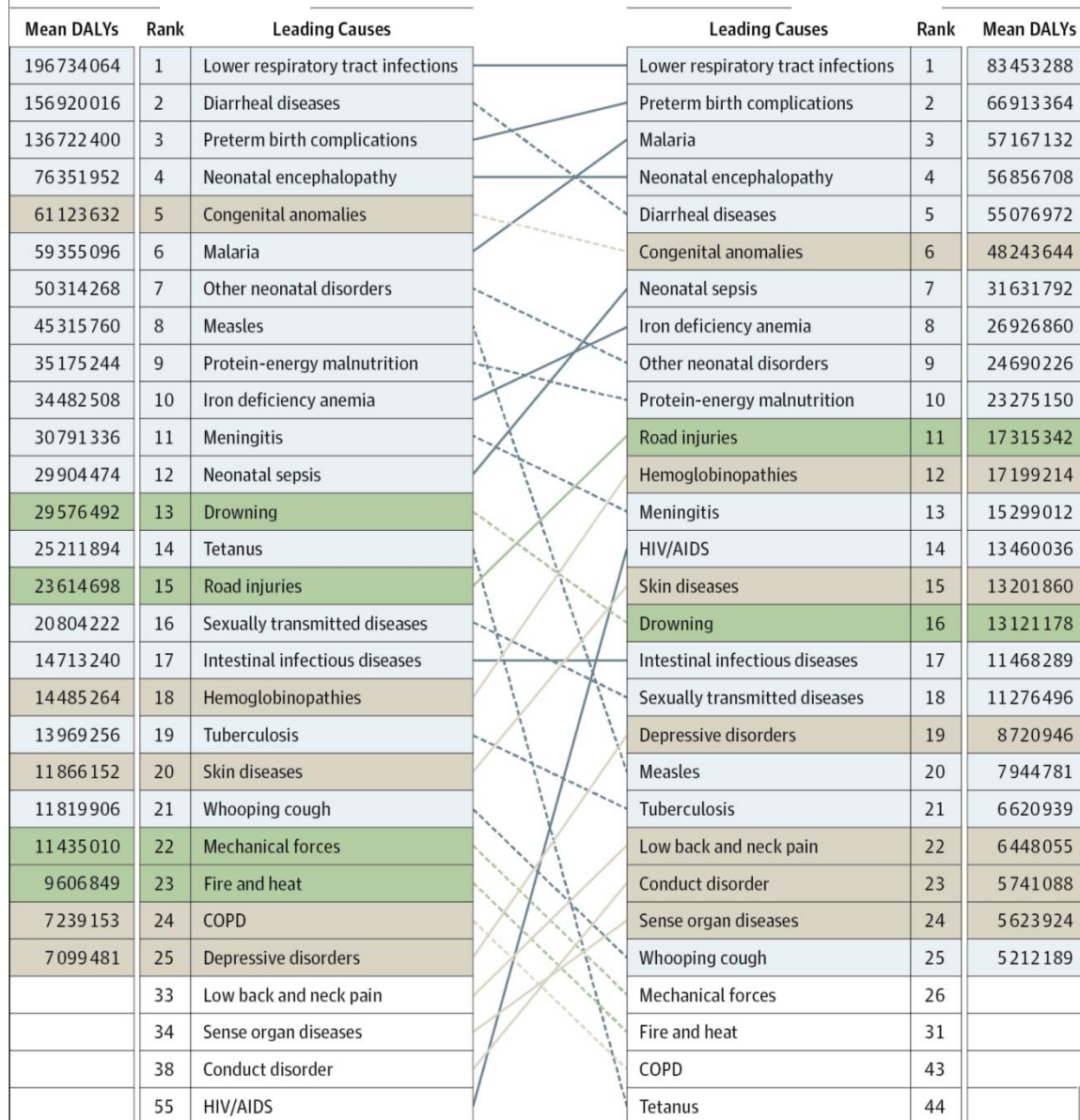
Walter Reed Army  
Institute of Research

Soldier Health • World Health



1990

2013



## Global and National Burden of Diseases and Injuries Among Children and Adolescents Between 1990 and 2013: Findings From the Global Burden of Disease 2013 Study

- Top 25 Global Causes of Disability-Adjusted Life-Years (DALYs) in Children and Adolescents Aged 0 to 19 Years, Both Sexes, 1990 and 2013
- Solid lines connecting the 1990 and 2013 charts indicate increased or unchanged rank; dotted lines, decreased rank

Communicable, maternal, neonatal, and nutritional

Noncommunicable

Injuries

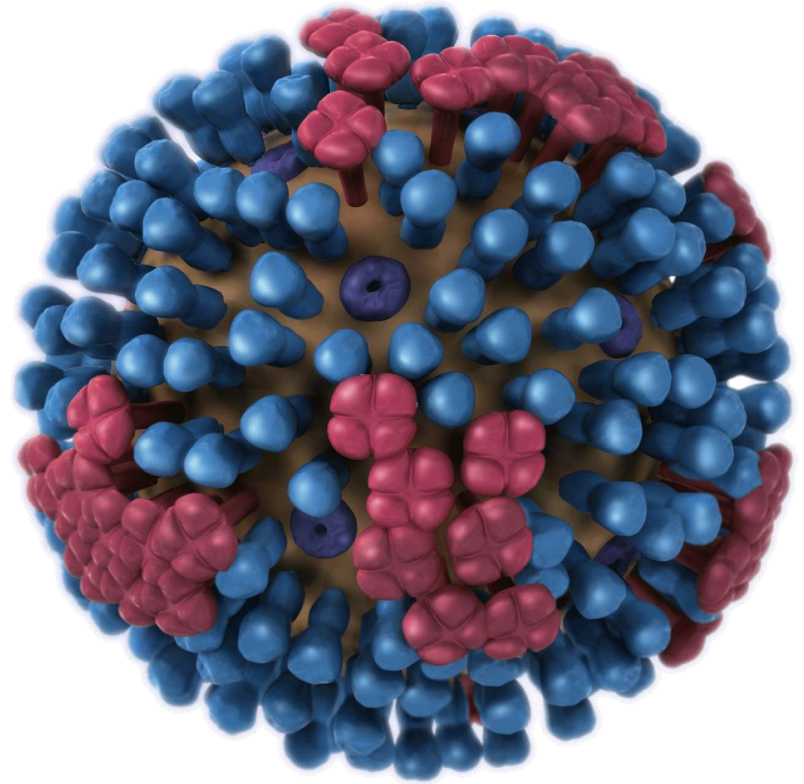
JAMA Pediatr. Published online January 25, 2016. doi:10.1001/jamapediatrics.2015.4276

# Influenza

- Seasonal
- Pandemic
- Avian

I had a little bird,  
And its name was Enza.  
I opened the window  
And in-flew-enza.\*

\*Children's skipping rhyme during the 1918 Spanish Influenza pandemic.



[www.cdc.gov](http://www.cdc.gov)

# Influenza Virus

- Family Orthomyxoviridae
- First isolated in 1933
- 8 single stranded, negative sense RNA molecules
- Encodes for 10 proteins
  - Nucleoprotein (NP), Matrix (M) protein
  - Important surface glycoproteins
    - Hemagglutinin
    - Neuraminidase

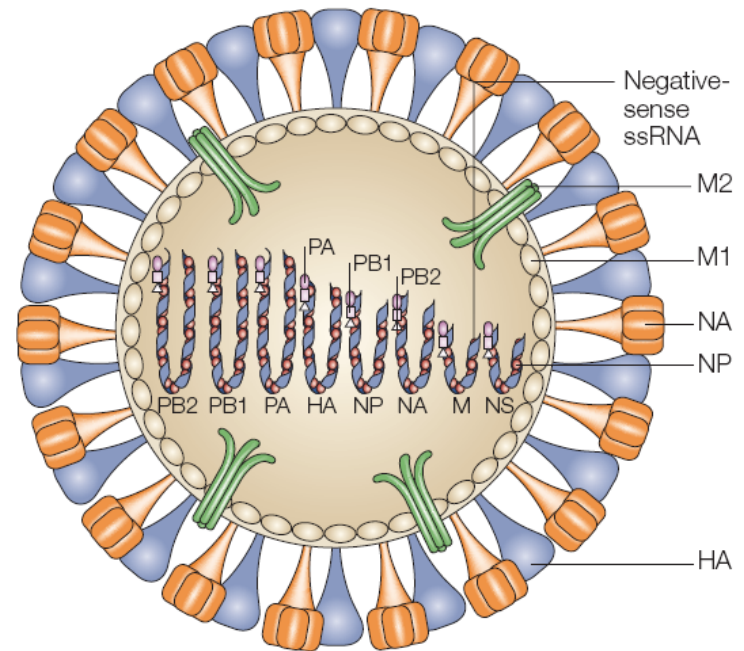


Figure 1 | **Schematic diagram of an influenza A virus virion.** Two surface glycoproteins, haemagglutinin (HA) and neuraminidase (NA), and the M2 ion-channel protein are embedded in the viral envelope, which is derived from the host plasma membrane. The ribonucleoprotein complex comprises a viral RNA segment associated with the nucleoprotein (NP) and three polymerase proteins (PA, PB1 and PB2). The matrix (M1) protein is associated with both ribonucleoprotein and the viral envelope. A small amount of non-structural protein 2 is also present, but its location within the virion is unknown.

# HA and NA

- Hemagglutinin (HA or H) initiates infection by binding to sialic acid residue on respiratory epithelial cells
- Neuraminidase (NA or N) liberates new virions after viral replication and help virions stay separated

# Case #1

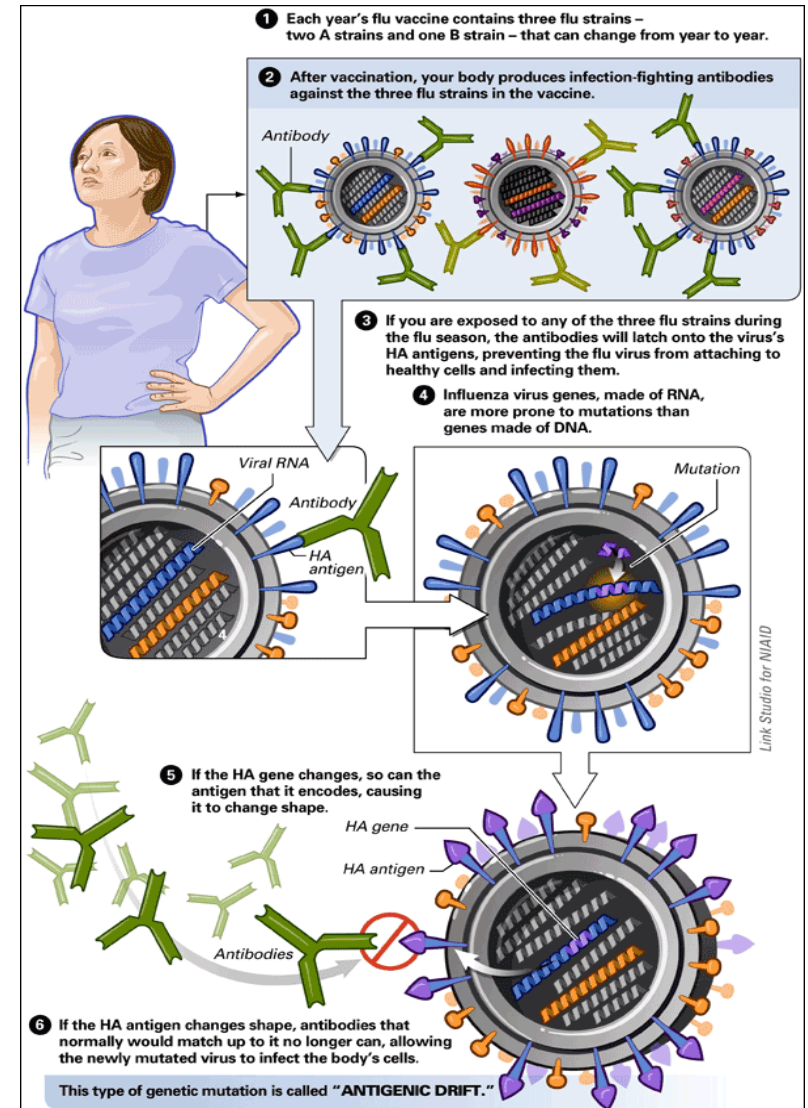
- You are deployed to the Philippines. You see a 24 yo male pig farmer with no medical history, previously in excellent health. The patient appears very ill, complaining of fevers, diffuse myalgias, cough, and shortness of breath. The patient requires intubation, but dies a week later. You hear of several other locals with similar symptoms, some young adults with severe disease.
- Pulmonary aspirates sent on your patient return from the lab in AFRIMS (Bangkok). Samples sent on 3 different days were negative on 2 of the days, and positive for Influenza A on a single sample. Confirmatory testing has not been able to determine the viral subtype.



# Antigenic Drift

- Occurs in influenza A and B
- Point mutations in the viral RNA genes
- Leads to production of slightly altered HA and NA
- **Annual occurrence** to avoid host immune system
- Results in less severe 'seasonal' epidemics
- Occurs as virus spreads through a susceptible population

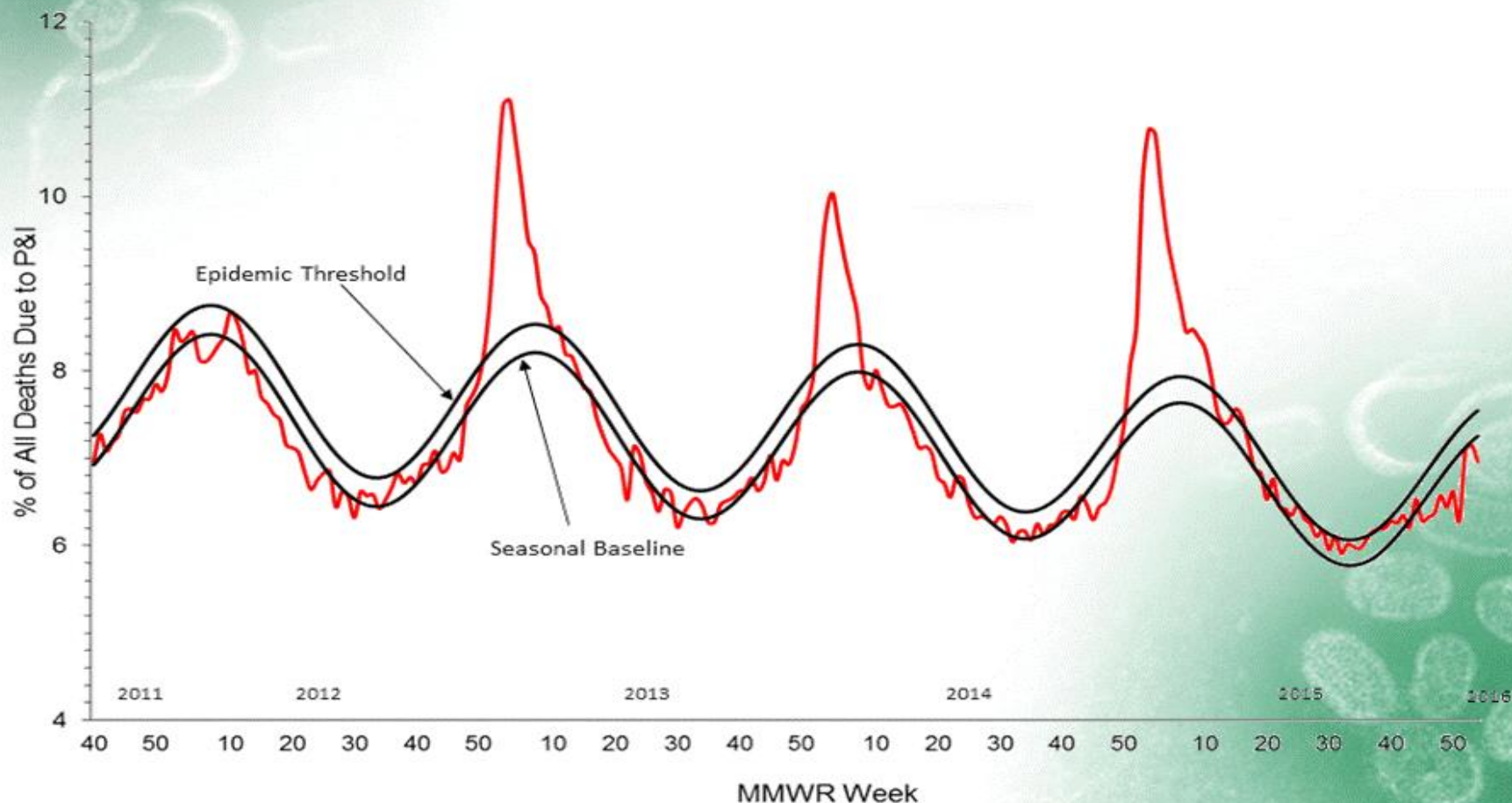
<http://nieman.harvard.edu/Microsites/NiemanGuideToCoveringPandemicFlu/TheScience/HowFluVirusesChange.aspx>



**A Weekly Influenza Surveillance Report Prepared by the Influenza Division**

## Pneumonia and Influenza Mortality from the National Center for Health Statistics Mortality Surveillance System

Data through the week ending January 16, 2016, as of February 4, 2016

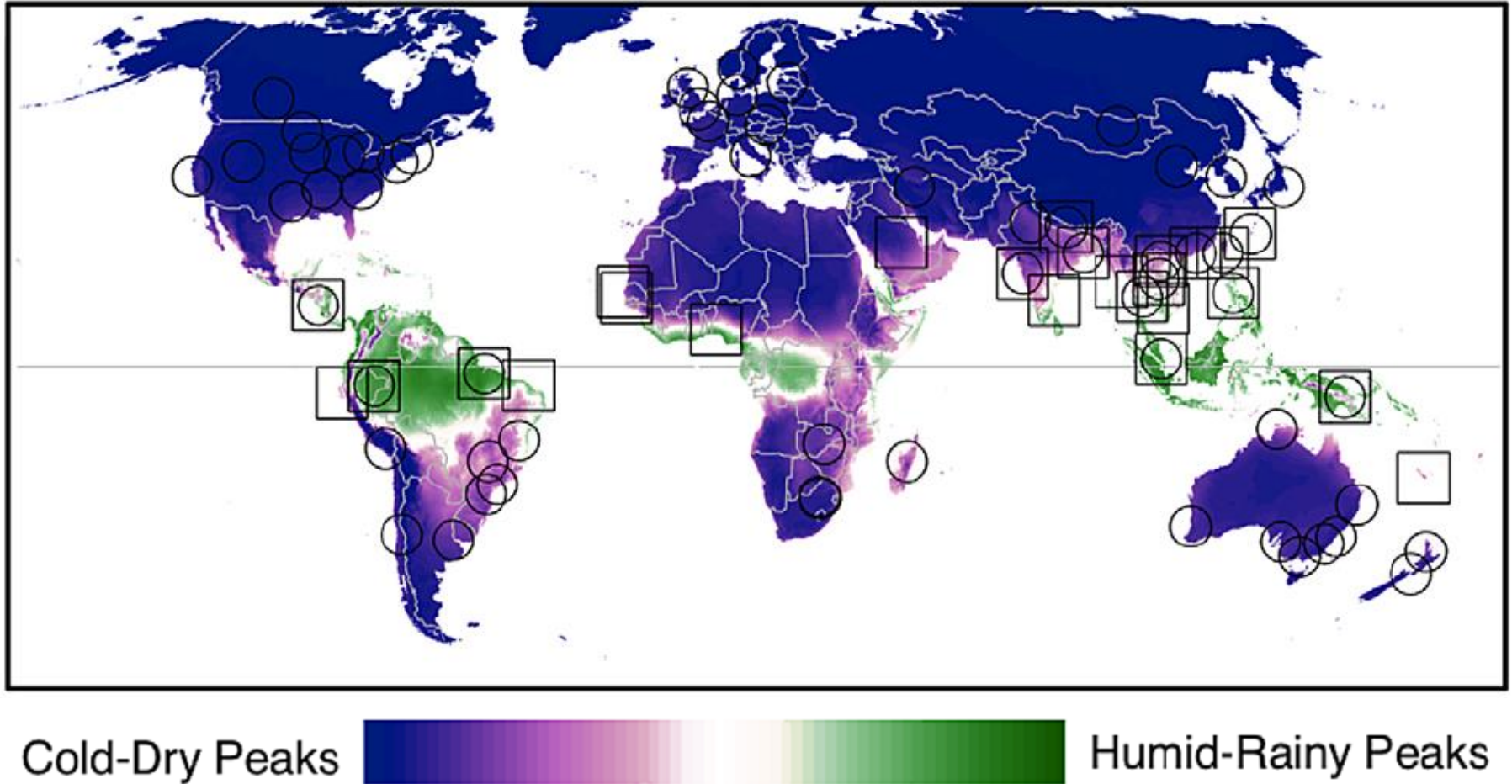




# Influenza in the Tropics

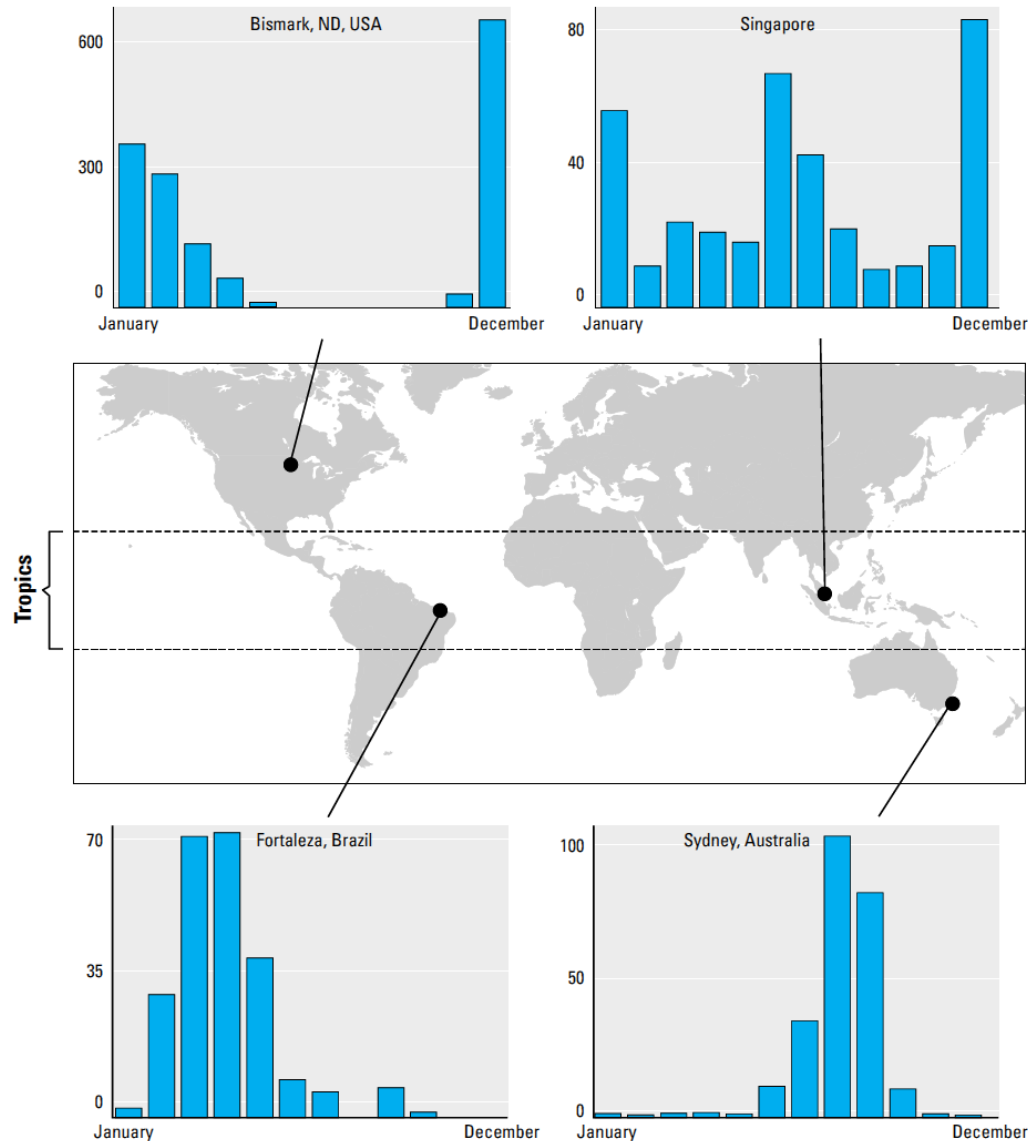
- Less distinct 'seasonal' pattern compared to temperate regions
- Year round infections
- 'Seasonal' patterns vary by location
  - Peaks related to rainy seasons
  - Biannual peaks (rainy season and winter months)
  - Year round infection without clear peaks

# Influenza in the Tropics



Tamerius et al. *Environ Health Perspect* 2011

# Seasonal Peaks Vary by Region



Tamerius et al.  
*Environ Health Perspect*, 2011

# Seasonal Influenza Vaccine

- Surveillance at 130 influenza centers in 101 countries
- WHO centers (Atlanta, London, Melbourne, Tokyo, Beijing)
- Meetings and decision for inclusion:
  - September for Southern hemisphere's vaccine
  - February for Northern hemisphere's vaccine
- WHO recommended 2015-2016 vaccine:
  - A/California/7/2009 (H1N1)pdm09-like virus
  - A/Switzerland/9715293/2013 (H3N2)-like virus (new strain for Northern Hemisphere)
  - B/Phuket/3073/2013-like virus (new strain for Northern Hemisphere)
  - B/Brisbane/60/2008-like virus
- Identify strain to be used, growing virus strain, quality control, production, sale, distribution, administration
  - TAKES TIME (at least 6 months) and MISMATCHES OCCUR

# Case #1

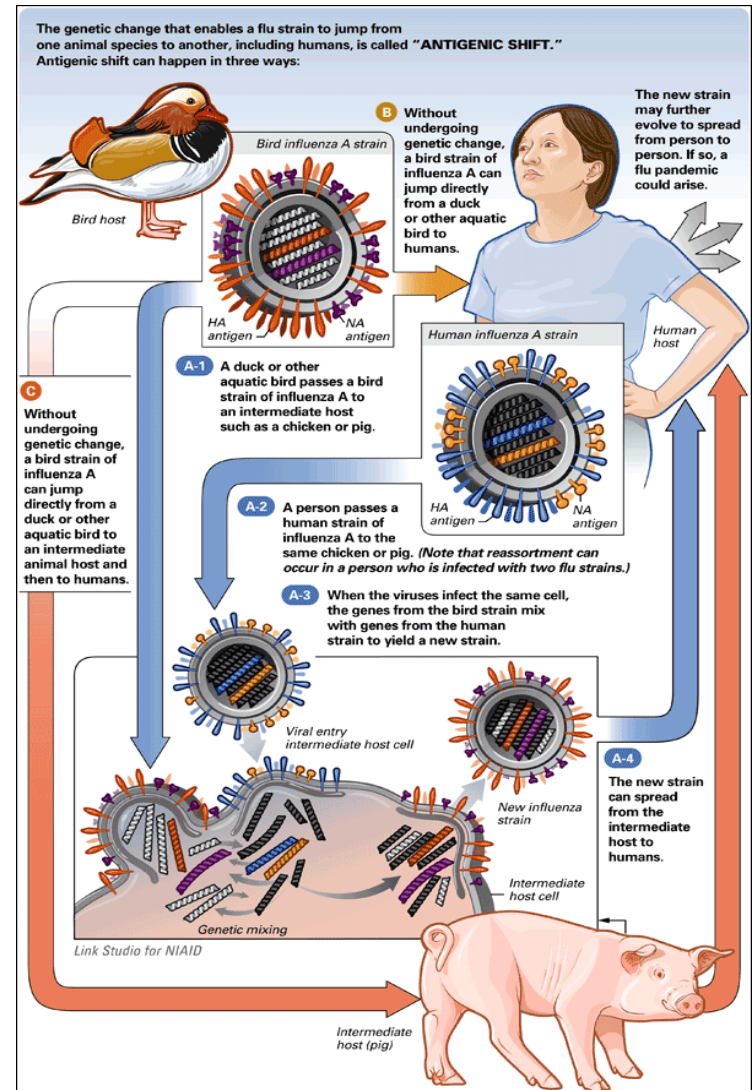
- You are deployed to the Philippines. You see a 24 yo male pig farmer with no medical history, previously in excellent health. The patient appears very ill, complaining of fevers, diffuse myalgias, cough, and shortness of breath. The patient requires intubation, but dies a week later. You hear of several other locals with similar symptoms, some young adults with severe disease.
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# Antigenic Shift





































- Major changes in HA and NA
- Occur in with influenza A (but not B)
- Reassortment of viral genetic material between viruses co-infecting the same cell
- May result in **Pandemic strains**
- Often little or no protective immunity in human hosts
- Usually spread more rapidly and cause more severe infection

<http://nieman.harvard.edu/Microsites/NiemanGuideToCoveringPandemicFlu/TheScience/HowFluVirusesChange.aspx>



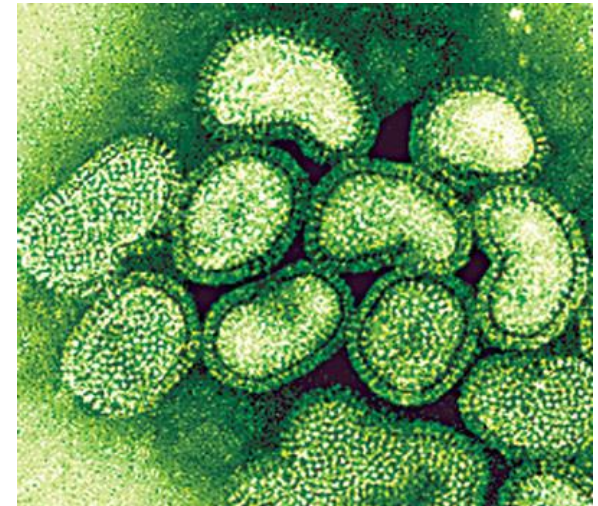
# HA and NA Diversity

- All HA and NA are found in birds
- Crossing of species is limited
  - Humans
    - H1, H2, H3
    - N1, N2
  - Horses
    - H3, H7
    - N7, N8
  - Pigs
    - H1, H3
    - N1, N2

Haemagglutinin subtypes			Neuraminidase subtypes				
H1				N1			
H2				N2			
H3				N3			
H4				N4			
H5				N5			
H6				N6			
H7				N7			
H8				N8			
H9				N9			
H10							
H11							
H12							
H13							
H14							
H15							

# Pandemic Influenza

- Influenza A virus introduction
  - Novel HA gene
  - No 'herd' immunity
  - Ability to spread efficiently among humans
- Pandemics of 20<sup>th</sup> century
  - All originated from avian influenza viruses
  - Intervals of 11-39 years
  - **1918 (H1N1: Spanish)**
  - 1957 (H2N2: Asian)
  - 1968 (H3N2: Hong Kong)
  - 2009 (H1N1: US, Mexico)
- Pseudo- and Abortive pandemics
  - 1947 (H1N1: Japan/Korea/New Jersey)
  - 1976 (H1N1: New Jersey)
  - 1977 (H1N1: Soviet Union)



# Pandemic Influenza

- Severe influenza syndrome
  - Fever, cough, fatigue, shortness of breath
  - Abdominal pain, diarrhea, vomiting
  - No conjunctivitis
- Chest X-ray with bilateral infiltration, lobar collapse, focal consolidation
- Complications
  - Acute respiratory distress, renal failure, bacterial superinfection



# 1918 H1N1 Influenza Pandemic

- 1/3 of the world's population infected
- Case fatality rates of >2.5%
- 3 waves: spring/summer, summer/fall, winter
- Unclear source of pandemic virus, limited capabilities

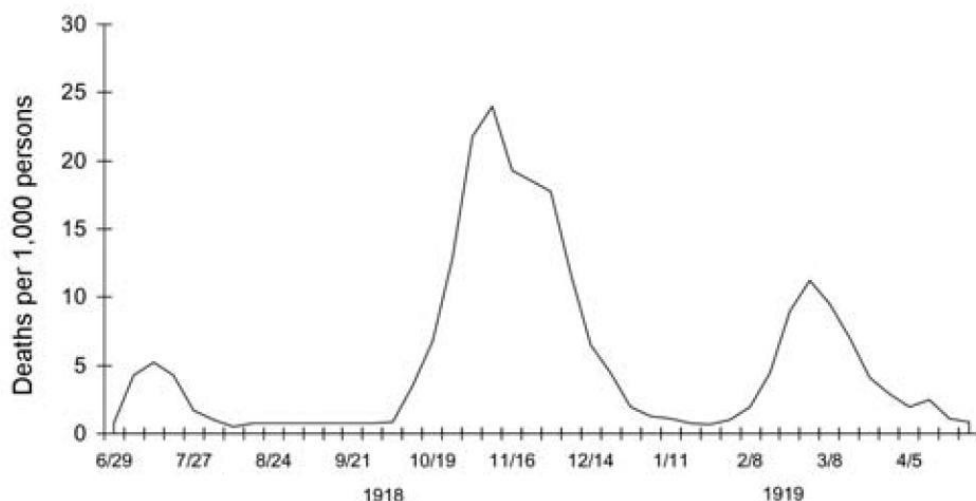


Figure 1. Three pandemic waves: weekly combined influenza and pneumonia mortality, United Kingdom, 1918–1919 (21).

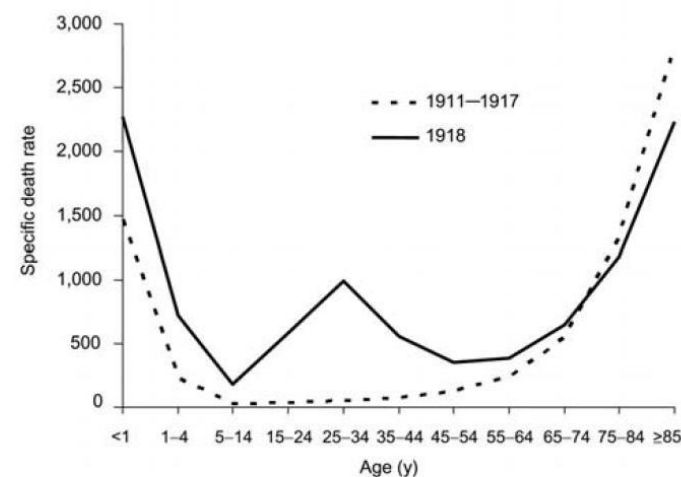


Figure 2. “U-” and “W-” shaped combined influenza and pneumonia mortality, by age at death, per 100,000 persons in each age group, United States, 1911–1918. Influenza- and pneumonia-specific death rates are plotted for the interpandemic years 1911–1917 (dashed line) and for the pandemic year 1918 (solid line) (33,34).



# 2009 H1N1 Pandemic

- 'Swine flu' first reported March 2009 in Mexico
- High human to human transmission, WHO pandemic level declared 6 June 2009
- Influenza A virus
  - Reassortment of 2 swine, one human, and one avian strain
- Incubation: 1-4 days; viral shedding peak: 2-3 day into illness
- Secondary attack rate: 14-19%

# 2009 H1N1 Pandemic

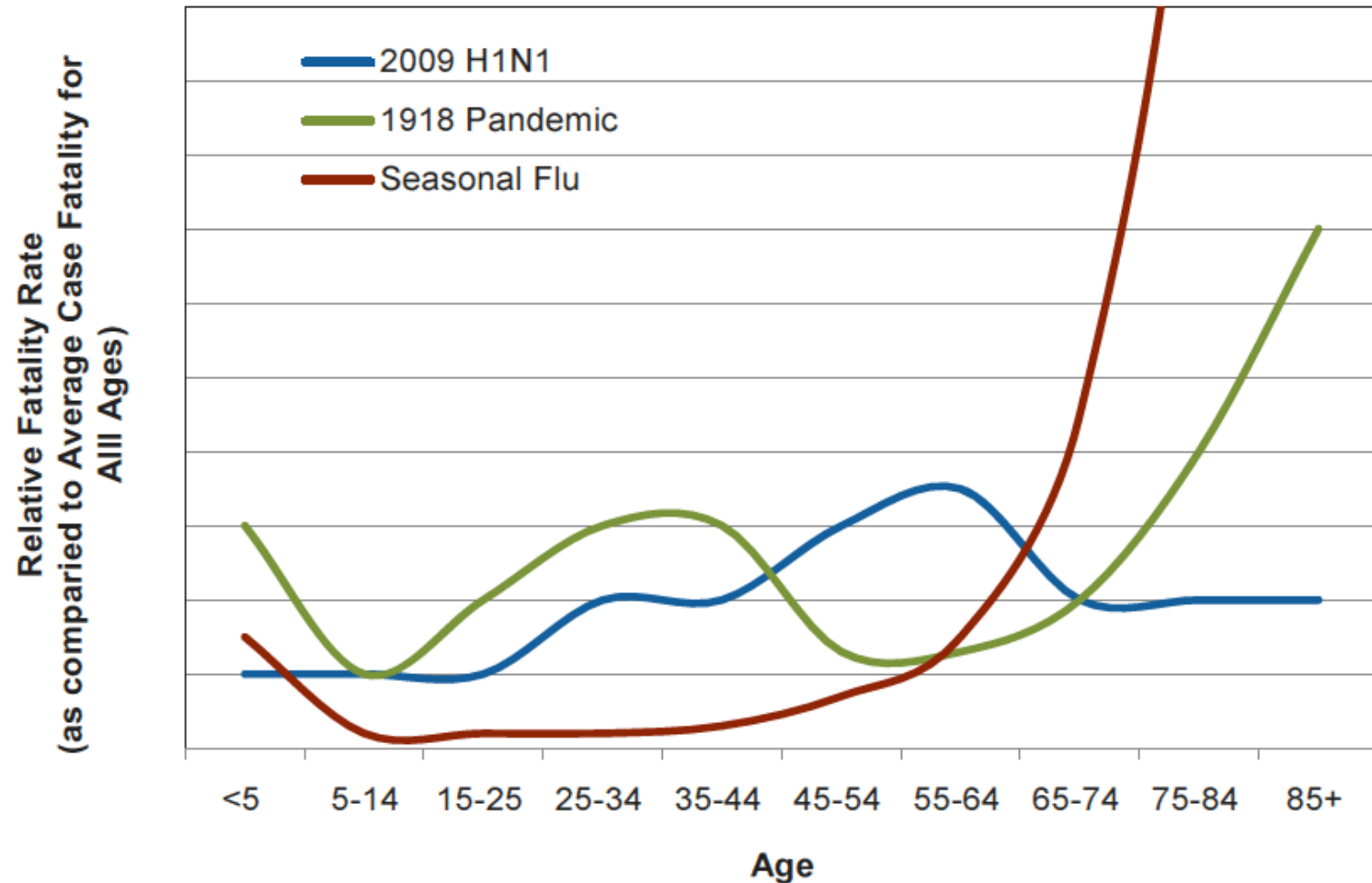


Figure 3: Age distribution of influenza mortality: comparing seasonal flu to the 1918 and 2009 pandemics

# 2009 H1N1 Pandemic

Table 2: Estimates of fatalities, hospitalizations, and cases for the 2009 H1N1 influenza pandemic, as modeled by RMS and estimated by the CDC as of February 13, 2010 (Data source: CDC, 2010a). Note: The CDC estimates are preliminary and do not represent the entire H1N1 pandemic. These numbers are expected to increase as more data becomes available.

Age	RMS Modeled Expected Value	CDC Lower Bound	CDC Upper Bound
<b>Fatalities</b>			
0-17 yrs	6,000	890	1,840
18-64 yrs	13,500	6,530	13,500
over 65 yrs	8,500	1,100	2,280
Total	28,000	8,520	17,620
<b>Hospitalizations</b>			
0-17 yrs	71,660	60,000	125,000
18-64 yrs	155,646	109,000	226,000
over 65 yrs	102,280	19,000	38,000
Total	329,586	188,000	389,000
<b>Cases</b>			
0-17 yrs	25,000,000	14,000,000	28,000,000
18-64 yrs	37,000,000	24,000,000	50,000,000
over 65 yrs	3,000,000	4,000,000	8,000,000
Total	65,000,000	42,000,000	86,000,000

# Avian Influenza

THE (A) LIST

## USDA

March Market Madness is on its Way.  
Are You Ready?!

03/03/2015 @ 11:50am

Massive Canal Project Seeks to  
Streamline Global Trade

03/04/2015 @ 2:49pm

◀ "Bird Flu" Confirmed in MN  
Commercial Turkey Flock

03/06/2015 @ 12:35pm



## MMWR™

Morbidity and Mortality Weekly Report



wordpress.com

**Outbreaks of Avian  
Influenza A (H5N2), (H5N8),  
and (H5N1) Among Birds —  
United States, December  
2014–January 2015**

Michael A. Jhung, MD,  
Deborah I. Nelson, PhD

# Avian Influenza

- Reservoir: Aquatic birds
- Direct and indirect transmission between birds (fecal aerosols, water, feed, etc.)
- Most isolates are not highly virulent but some result in epidemics with high mortality in bird populations
- On rare occasions, direct transmission to humans



# Cumulative Numbers of Confirmed Human H5N1 Avian Influenza reported to the WHO (as of January 2016)

Country	2003-2009*		2010		2011		2012		2013		2014		2015		Total	
	cases	deaths	cases	deaths	cases	deaths	cases	deaths	cases	deaths	cases	deaths	cases	deaths	cases	deaths
Azerbaijan	8	5	0	0	0	0	0	0	0	0	0	0	0	0	8	5
Bangladesh	1	0	0	0	2	0	3	0	1	1	0	0	0	0	8	1
Cambodia	9	7	1	1	8	8	3	3	26	14	9	4	0	0	56	37
Canada	0	0	0	0	0	0	0	0	1	1	0	0	0	0	1	1
China	38	25	2	1	1	1	2	1	2	2	2	0	5	1	53	31
Djibouti	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0
Egypt	90	27	29	13	39	15	11	5	4	3	37	14	136	39	346	116
Indonesia	162	134	9	7	12	10	9	9	3	3	2	2	2	2	199	167
Iraq	3	2	0	0	0	0	0	0	0	0	0	0	0	0	3	2
Lao People's Democratic Republic	2	2	0	0	0	0	0	0	0	0	0	0	0	0	2	2
Myanmar	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0
Nigeria	1	1	0	0	0	0	0	0	0	0	0	0	0	0	1	1
Pakistan	3	1	0	0	0	0	0	0	0	0	0	0	0	0	3	1
Thailand	25	17	0	0	0	0	0	0	0	0	0	0	0	0	25	17
Turkey	12	4	0	0	0	0	0	0	0	0	0	0	0	0	12	4
Viet Nam	112	57	7	2	0	0	4	2	2	1	2	2	0	0	127	64
<b>Total</b>	<b>468</b>	<b>282</b>	<b>48</b>	<b>24</b>	<b>62</b>	<b>34</b>	<b>32</b>	<b>20</b>	<b>39</b>	<b>25</b>	<b>52</b>	<b>22</b>	<b>143</b>	<b>42</b>	<b>846</b>	<b>449</b>

\* 2003-2009 total figures. Breakdowns by year available on next table

Total number of cases includes number of deaths  
WHO reports only laboratory cases  
All dates refer to onset of illness

Source: WHO/GIP, data in HQ as of 20 January 2016



**Table 3. Presentation and Outcomes among Patients with Confirmed Avian Influenza A (H5N1).\***

Outcome or Measure	Hong Kong, 1997 (N=18)	Thailand, 2004 (N=17)	Vietnam, 2004 (N=10)	Ho Chi Minh City, 2005 (N=10)	Cambodia, 2005 (N=4)
Age — yr					
Median	9.5	14	13.7†	19.4†	22
Range	1–60	2–58	5–24	6–35	8–28
Male sex — no. (%)	8 (44)	9 (53)	6 (60)	3 (30)	1 (25)
Time from last presumed exposure to onset of illness — days					
Median	NS	4	3	NS	NS
Range		2–8	2–4		
No. of family clusters		1	2	1	1
Patients with exposure to ill poultry — no./total no. (%)	11/16 (70) visited poultry markets	14/17 (82)	8/9 (89)	6/6 (100) Status of 4 unknown	3/4 (75)
Time from onset of illness to presentation or hospitalization — days					
Median	3	NS	6	6	8‡
Range	1–7		3–8	4–7	5–8
Clinical presentation — no./total no. (%)					
Fever (temperature >38°C)	17/18 (94)	17/17 (100)	10/10 (100)	10/10 (100)	4/4 (100)
Headache	4/18 (22)	NS	NS	1/10 (10)	4/4 (100)
Myalgia	2/18 (11)	9/17 (53)	0	2/10 (20)	NS
Diarrhea	3/18 (17)	7/17 (41)	7/10 (70)	NS	2/4 (50)
Abdominal pain	3/18 (17)	4/17 (24)	NS	NS	2/4 (50)
Vomiting	6/18 (33)	4/17 (24)	NS	1/10 (10)	0
Cough§	12/18 (67)	16/17 (94)	10/10 (100)	10/10 (100)	4/4 (100)
Sputum	NS	13/17 (76)	5/10 (50)	3/10 (30)	NS
Sore throat	4/12 (33)	12/17 (71)	0	0	1/4 (25)
Rhinorrhea	7/12 (58)	9/17 (53)	0	0	NS
Shortness of breath§	1/18 (6)	13/17 (76)	10/10 (100)	10/10 (100)	NS
Pulmonary infiltrates	11/18 (61)	17/17 (100)	10/10 (100)	10/10 (100)	4/4 (100)
Lymphopenia¶	11/18 (61)	7/12 (58)	NS	8/10 (80)	1/2 (50)
Thrombocytopenia	NS	4/12 (33)	NS	8/10 (80)	1/2 (50)
Increased aminotransferase levels	11/18 (61)	8/12 (67)	5/6 (83)	7/10 (70)	NS

N ENGL J MED 353;13 WWW.NEJM.ORG SEPTEMBER 29, 2005

# Clinical Presentation of H5N1 Infection in Humans

- Typically younger
- Short incubation period
- High level of poultry exposure
- **Common Symptoms:**
  - Fever
  - Cough
  - Runny nose
  - Shortness of breath
  - Abnormal CXR
  - Low lymphocytes
  - Low platelets
  - Increased AST/ALT

# Severe Illness from H5N1

Outcome or Measure	Hong Kong, 1997 (N=18)	Thailand, 2004 (N=17)	Vietnam, 2004 (N=10)	Ho Chi Minh City, 2005 (N=10)	Cambodia, 2005 (N=4)
Hospital course — no. (%)					
Respiratory failure	8 (44)	13 (76)	9 (90)	7 (70)	4 (100)
Cardiac failure	NS	7 (41)	NS	0	NS
Renal dysfunction	4 (22)	5 (29)	1 (10)	2 (20)	NS
Antiviral therapy					
Amantadine	10 (56)	0	0	0	NS
Ribavirin	1 (6)	0	2 (20)	0	
Oseltamivir	0	10 (59)	5 (50)	10 (100)	
Corticosteroids**	5 (28)	8 (47)	7 (70)	5 (50)	NS
Inotropic agents	NS	8 (47)	2 (20)	NS	
Time from onset of illness to death — days					
Median	23	12	9	12.8†	8
Range	8–29	9–30	4–17	4–21	6–10
Deaths — no. (%)	6 (33)	12 (71)	8 (80)	8 (80)	4 (100)

# H5N1 Transmission

**Table 2.** Serologic and Clinical Characteristics of Avian Influenza A (H5N1) Infection among Contacts of Patients or Infected Animals.\*

Group	Location	Year	Assay Method†	No. Tested	No. (%) Positive	Comment	Reference
Household contacts	Hong Kong	1997	MN, ELISA, WB	51	6 (12)	Concurrent exposure to poultry in 5 of 6 positive household contacts; 0 of 9 non-household contacts positive	Katz et al. <sup>8</sup>
Tour group contacts				26	1 (4)		
Workplace contacts				47	0		
Poultry cullers	Hong Kong	1997	MN, WB	293	9 (3)	Seroconversion in 1 with mild acute respiratory illness	Bridges et al. <sup>7</sup>
Poultry-market workers	Hong Kong	1997	MN, WB	1525	— (estimated 10%)	Most asymptomatic	Bridges et al. <sup>7</sup>
Health care workers with contact	Hong Kong	1997	MN, WB	217	8 (4)‡	Seroconversion in 2; most asymptomatic	Buxton Bridges et al. <sup>9</sup>
Household contacts§	Vietnam	2004	MN	51	0	0 of 83 controls positive	
Contacts of sick poultry§	Vietnam	2004	MN	25	0	—	
Health care workers with contact	Vietnam	2004	MN	83	0	2 with suspected illness (not confirmed)	Liem et al. <sup>10</sup>
Health care workers with contact	Vietnam	2004	MN, RT-PCR	60	0	No recognized illness	Schultsz et al. <sup>11</sup>
Health care workers with contact§	Thailand	2004	Clinical only	54	0	No recognized illness	
Health care workers with contact	Thailand	2004	Clinical only	35	0	No fever or influenza-like illness	Apisarnthanarak et al. <sup>12</sup>
Poultry cullers§	Indonesia	2005	MN	79	1 (1)	Asymptomatic	

\* Some serologic surveys of apparent human-to-human transmission may have been confounded by concurrent exposure to ill poultry.

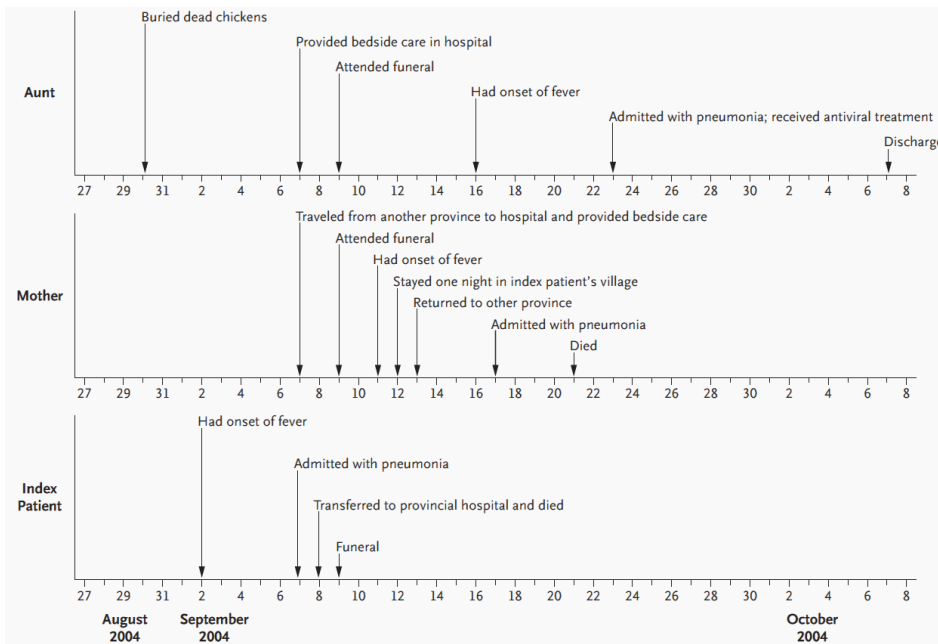
† MN denotes identification of serum antibody against influenza A (H5N1) by microneutralization, ELISA enzyme-linked immunosorbent assay, WB detection of influenza A (H5)—specific bands by Western blotting, and RT-PCR reverse-transcriptase–polymerase-chain-reaction assay for viral RNA.

‡ P=0.01 for the comparison with 2 of 309 health care workers without contact (0.6 percent).

§ Data are from the WHO Meeting on Case Management and Research on Human Influenza A (H5) held in Hanoi, May 10 through 12, 2005.

## Probable Person-to-Person Transmission of Avian Influenza A (H5N1)

N ENGL J MED 352;4 WWW.NEJM.ORG JANUARY 27, 2005



- A few reports of probable transmission among close family or hospital contacts
- WHO: limited non-sustained human-to-human spread



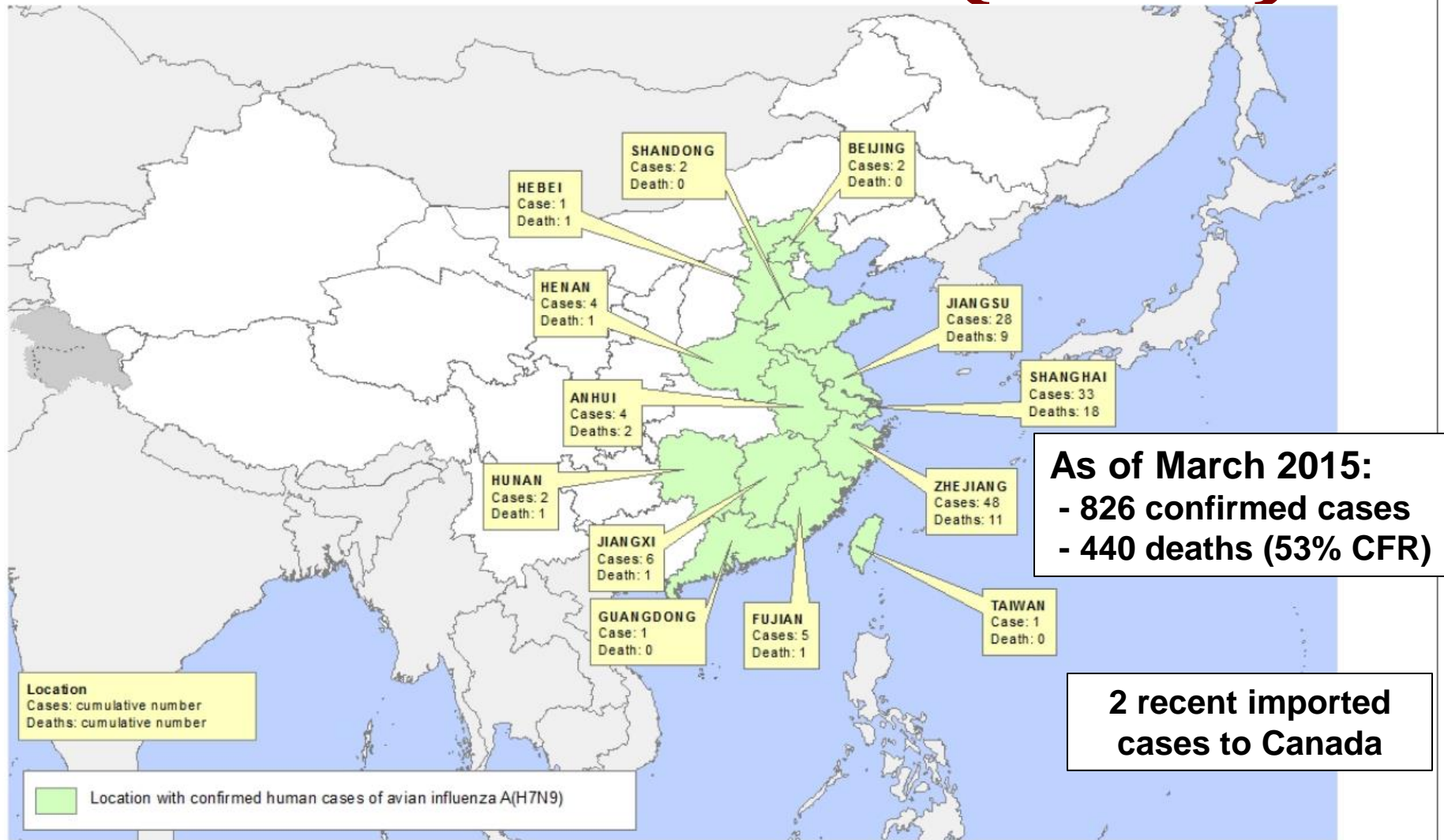
# Avian Influenza

Table 1. Direct transmission of avian influenza viruses to humans

Virus subtype	Year	Location	No. cases (no. deaths)	Clinical features	Notes	Reference(s)
H5N1	1997	Hong Kong	18 (6)		Associated with outbreak of highly pathogenic AI in poultry in the region	(5,6)
H9N2	1999	Hong Kong	2 (0)	Mild influenzalike illness		(7)
H9N2	1999	Guangdong Province, China	5 (0)	Mild influenzalike illness		(8)
H9N2	2003	Hong Kong	1 (0)	Mild influenzalike illness		(9)
H5N1	2003	Hong Kong	2 (1)	Primary viral pneumonia, lymphopenia, respiratory distress	7-year-old girl died in Fujian Province, China, and H5N1 infection was not confirmed. Her 33-year-old father died from confirmed H5N1 influenza infection in Hong Kong, and her 8-year-old brother recovered from H5N1 infection.	(10)
H7N7	2003	Netherlands	89 (1)	Conjunctivitis (78 cases), mild influenzalike symptoms (2 cases) or both (5 cases). In fatal case, pneumonia followed by respiratory distress syndrome	Most cases were in persons involved in handling poultry (86), with 3 family members also affected.	(11)
H10N7	2004	Egypt	2 (0)	Fever and cough	Both cases were in infants, who recovered without complications	(12)
H5N1	2003–present	Asia (Vietnam, Thailand, Cambodia, Indonesia)	116 (60)*	Fever, respiratory symptoms, lymphopenia, elevated liver enzymes. Severe cases progress to respiratory failure, multiple organ dysfunction, and death.	Human cases concomitant with unprecedented outbreaks of highly pathogenic H5N1 AI in poultry	WHO* (13–15)

\*WHO, World Health Organization. As of September 29, 2005. Source: [http://www.who.int/csr/disease/avian\\_influenza/country/en](http://www.who.int/csr/disease/avian_influenza/country/en)

# Avian Influenza A (H7N9)

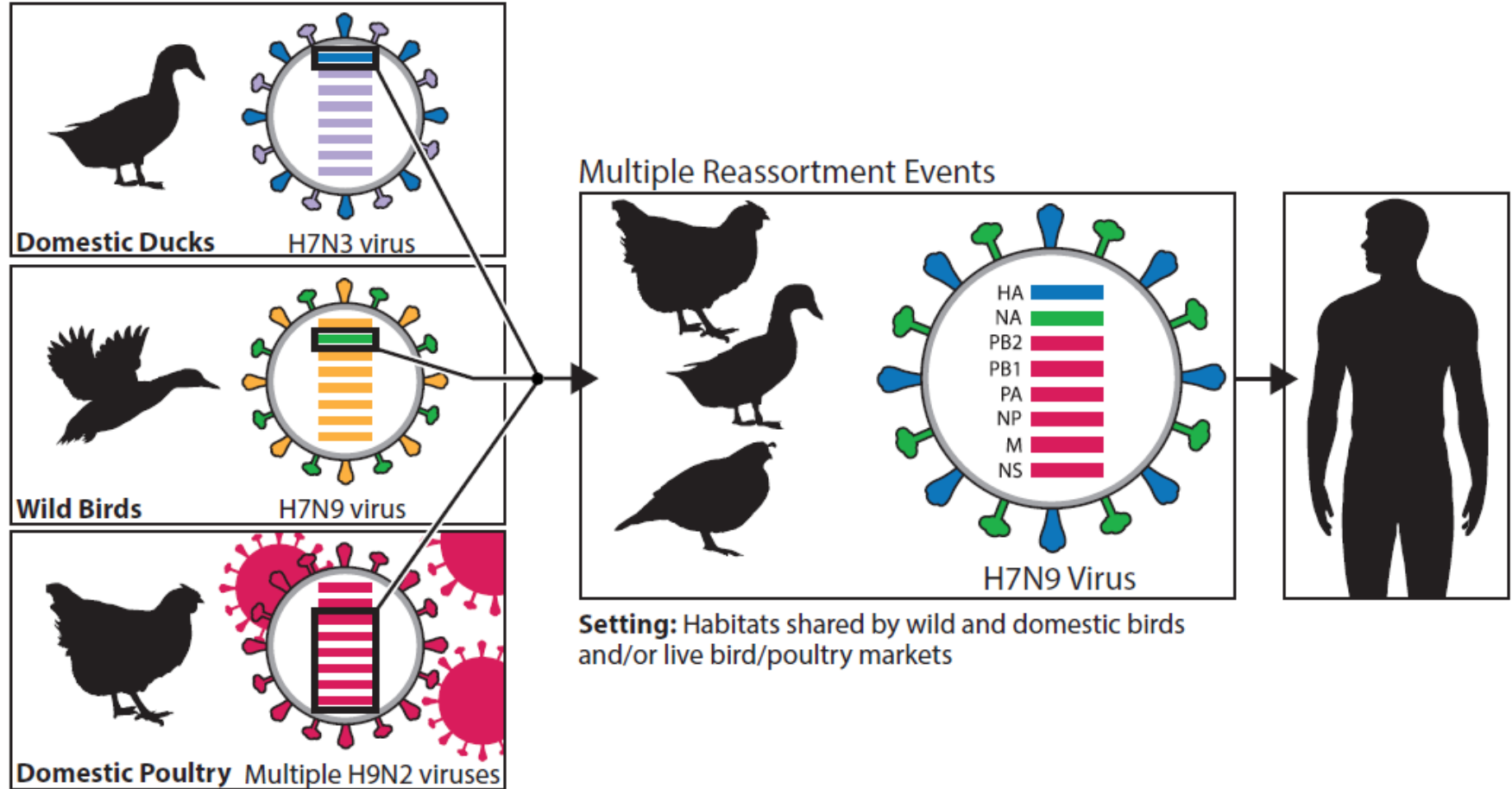


Data as of 25 October 2013, 8:00 GMT+1  
Source: WHO/GIP

The designations employed and the presentation of the material in this publication do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not be full agreement.  
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# Genetic Evolution of H7N9 Virus in China, 2013



Centers for Disease  
Control and Prevention  
National Center for Immunization  
and Respiratory Diseases

# Avoid These....

**Table 4. Exposures That May Put a Person at Risk for Infection with Influenza A (H5N1).\***

**Countries and territories where influenza A (H5) viruses have been identified as a cause of illness in human or animal populations since October 1, 2003**

During the 7 to 14 days before the onset of symptoms, one or more of the following:

- Contact (within 1 m) with live or dead domestic fowl or wild birds or domestic ducks
- Exposure to settings in which domestic fowl were confined or had been confined in the previous 6 weeks
- Unprotected contact (within touching or speaking distance) with a person for whom the diagnosis of influenza A (H5N1) is confirmed or being considered
- Unprotected contact (within touching or speaking distance, 1 m) with a person with an unexplained acute respiratory illness that later resulted in severe pneumonia or death
- Occupational exposure†

**Countries and territories where influenza A (H5) viruses have not been identified as a cause of illness in human or animal populations since October 1, 2003**

During the 7 to 14 days before the onset of symptoms, close contact with an ill traveler from one of the areas with known influenza A (H5) activity, history of travel to a country or territory with reported avian influenza activity due to influenza A (H5N1) in the animal populations, or living in an area in which there are rumors of the death of domestic fowl, and one or more of the following:

- Contact (within 1 m) with live or dead domestic fowl or wild birds in any setting or with domestic ducks
- Exposure to settings in which domestic fowl were confined or had been confined in the previous 6 weeks
- Contact (within touching or speaking distance) with a patient with a confirmed case of influenza A (H5)
- Contact (within touching or speaking distance) with a person with an unexplained acute respiratory illness that later resulted in severe pneumonia or death
- Occupational exposure†



Figure 2. The effect of highly pathogenic H5N1 virus on ducklings in Vietnam (photo T Tumpey).

\* These summaries do not present formal WHO guidelines, although they contain content from WHO documents.<sup>1</sup>

† At-risk occupations include domestic-fowl worker, worker in a domestic-fowl processing plant, domestic-fowl culler (catching, bagging, or transporting birds or disposing of dead birds), worker in a live-animal market, chef working with live or recently killed domestic fowl, dealer or trader in pet birds, health care worker, and a worker in a laboratory processing samples possibly containing influenza A (H5N1) virus.

# Pandemic & Avian Influenza: Management

- Early suspicion and recognition
- Isolation and testing
- Symptom management
- Neuraminidase inhibitors
  - Oseltamivir (oral), zanamivir (inhaled), and peramivir (IV)
  - Effective for both influenza A and B (unlike amantadine)
  - Give within 48 hr of symptom onset
  - Prevention of H5N1 but resistance develops rapidly
- Vaccine if available
  - Pandemic H1N1 influenza vaccine in 2009-2010
  - H5N1 avian influenza vaccine manufactured by Sanofi Pasteur approved by FDA in 2007
  - Testing H7N9 avian influenza vaccine (NIH sponsored)

## **Good Rule of Thumb:**

Severe Respiratory Disease → isolate patient until you know you're dealing with

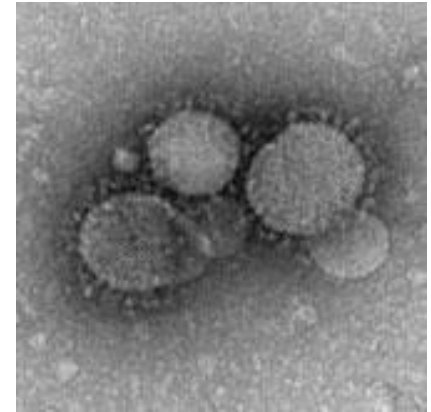
# Oseltamivir Prophylaxis

- CDC dose NOT recommend widespread prophylaxis use
- Vaccination and close monitoring as alternative
- 70-90% effective
- **75 mg once daily, exposure time + 7 days**
  - Likely not helpful to start > 48 hrs since exposure
  - 2 weeks after last case in long-term care facilities



# Coronaviruses

- Meaning 'crown or halo'
- Large, positive sense RNA virus
- Family *Coronaviridae*
- Infect humans, mammals, birds
- **Severe acute respiratory syndrome (SARS-CoV)**
  - Rapid human to human spread worldwide
  - 774 probable deaths, 10% fatality rate
  - Started in Hong Kong Feb. 2003
    - Civet cats and other small mammals to humans?
  - Delayed peak transmission period
    - Rare within first 5 days of symptom onset
    - Easier recognition, isolation, and interruption
  - **No cases since 2004**

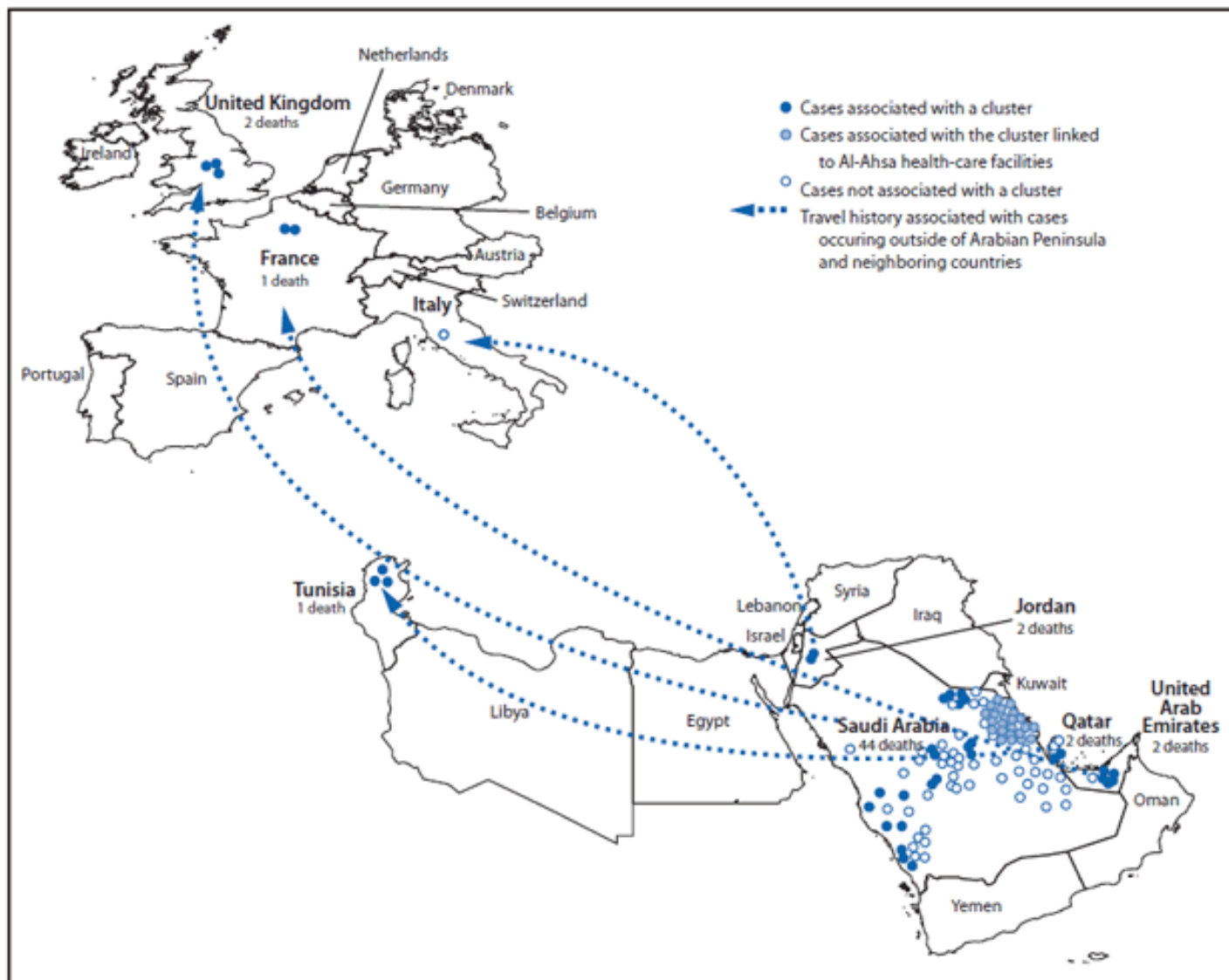


CDC Image



# Middle East Respiratory Syndrome (MERS-CoV)

- Zoonotic virus first identified in humans in 2012
- Reservoir: bats → **camels** → humans
- Sporadic introduction into humans with some human-to-human transmission among close contacts
  - Clusters within families
  - Nosocomial transmission
- Range of symptoms from asymptomatic to severe/fatal respiratory illness
- 587 deaths in 1,638 lab confirmed cases (36% CFR) as of FEB 2016



CDC MMWR Sept 27, 2013, 62(38); 793-6

# Epidemiological, demographic, and clinical characteristics of 47 cases of Middle East respiratory syndrome coronavirus disease from Saudi Arabia: a descriptive study

*Lancet Infect Dis* 2013;  
13: 752–61

Abdullah Assiri\*, Jaffar A Al-Tawfiq\*, Abdullah A Al-Rabeeh, Fahad A Al-Rabiah, Sami Al-Hajjar, Ali Al-Barrak, Hesham Flemban, Wafa N Al-Nassir, Hanan H Balkhy, Rafat F Al-Hakeem, Hatem Q Makhdoom, Alimuddin I Zumla\*, Ziad A Memish\*

	Patients (n=47)
Fever	46 (98%)
Fever with chills or rigors	41 (87%)
Cough	39 (83%)
Dry	22 (47%)
Productive (sputum)	17 (36%)
Haemoptysis	8 (17%)
Shortness of breath	34 (72%)
Chest pain	7 (15%)
Sore throat	10 (21%)
Runny nose	2 (4%)
Abdominal pain	8 (17%)
Nausea	10 (21%)
Vomiting	10 (21%)
Diarrhoea	12 (26%)
Myalgia	15 (32%)
Headache	6 (13%)

**Table 3: Symptoms of Middle East respiratory syndrome in 47 Saudi cases at presentation**

	Patients (n=47)	Deaths (%)*
Any comorbidity	45 (96%)	28 (60%)
Diabetes	32 (68%)	21 (66%)
Chronic kidney disease	23 (49%)	17 (74%)
Chronic heart disease	13 (28%)	10 (77%)
Hypertension	16 (34%)	13 (81%)
Chronic lung disease	12 (26%)	10 (83%)
Obesity	8 (17%)	5 (63%)
Smoking	11 (23%)	7 (64%)
Malignant disease	1 (2%)	1 (100%)
Steroid use	3 (6%)	3 (100%)

\*Proportion of patients who died according to comorbidity.


**Table 4: Comorbidities in 47 Saudi cases of Middle East respiratory syndrome**


Overall CFR = 36%  
Any comorbidity = 60%

# Korea MERS cases at 180; studies note outbreak patterns

Filed Under: **MERS-CoV**

Lisa Schnirring | Staff Writer | CIDRAP News | Jun 25, 2015

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- 89% cases traced to 3 hospital-linked ‘super-spreading’ events
- Pattern resembles Middle East cases
  - Spread is slow beyond hospital-linked cases
- Incubation times longer in tertiary infected compared to those secondarily infected
- Better patient contact tracing could have prevented spread

# Current Guidance – MERS-CoV

- All cases linked to travel or residence in affected areas
- Assess risk, suspect disease
- Lower respiratory tract specimen for rRT-PCR preferred
  - Nasopharyngeal wash or swabs
  - Serum for PCR and serologic testing
  - Stool for PCR
- Follow up serology testing
- Isolation Precautions
  - Airborne for suspected cases
    - For SARS, CDC: 'airborne precaution preferred'
  - Other standard AND contact precautions



N95 Mask

# Current Guidance – MERS-CoV

- **PATIENT UNDER INVESTIGATION (PUI) PER CDC WEBSITE:**

- FEVER AND PNEUMONIA OR ARDS AND:

- A HISTORY OF TRAVEL FROM COUNTRIES IN OR NEAR THE ARABIAN PENINSULA WITHIN 14 DAYS BEFORE SYMPTOM ONSET, OR
- CLOSE CONTACT WITH A SYMPTOMATIC TRAVELER WHO DEVELOPED FEVER AND ACUTE RESPIRATORY ILLNESS (NOT NECESSARILY PNEUMONIA) WITHIN 14 DAYS AFTER TRAVELING FROM COUNTRIES IN OR NEAR THE ARABIAN PENINSULA<sup>1</sup> OR
- A MEMBER OF A CLUSTER OF PATIENTS WITH SEVERE ACUTE RESPIRATORY ILLNESS (E.G., FEVER AND PNEUMONIA REQUIRING HOSPITALIZATION) OF UNKNOWN ETIOLOGY IN WHICH MERS-COV IS BEING EVALUATED, IN CONSULTATION WITH STATE AND LOCAL HEALTH DEPARTMENTS.

OR

- FEVER AND SYMPTOMS OF RESPIRATORY ILLNESS AND BEING IN A HEALTHCARE FACILITY WITHIN 14 DAYS BEFORE SYMPTOM ONSET IN A COUNTRY OR TERRITORY IN OR NEAR THE ARABIAN PENINSULA IN WHICH RECENT HEALTHCARE-ASSOCIATED CASES OF MERS HAVE BEEN IDENTIFIED.





# Measles

- **Highly contagious (AIRBORNE transmission); contagious up to 4 days prior to onset of rash**
- **Typical presentation**
  - High fever, cough, runny nose, conjunctivitis
  - Rash erupting a few days later; spreads from face and head downward
- **Complications**
  - Ear infections in 10% (can result in hearing loss)
  - Diarrhea (10%)
  - Pneumonia (5%) – **most common cause of death**
  - Encephalitis (0.1%) – can result in major neurologic sequelae
  - ~25% require hospitalization
  - Mortality: 1-2 per 1,000; higher if malnourished

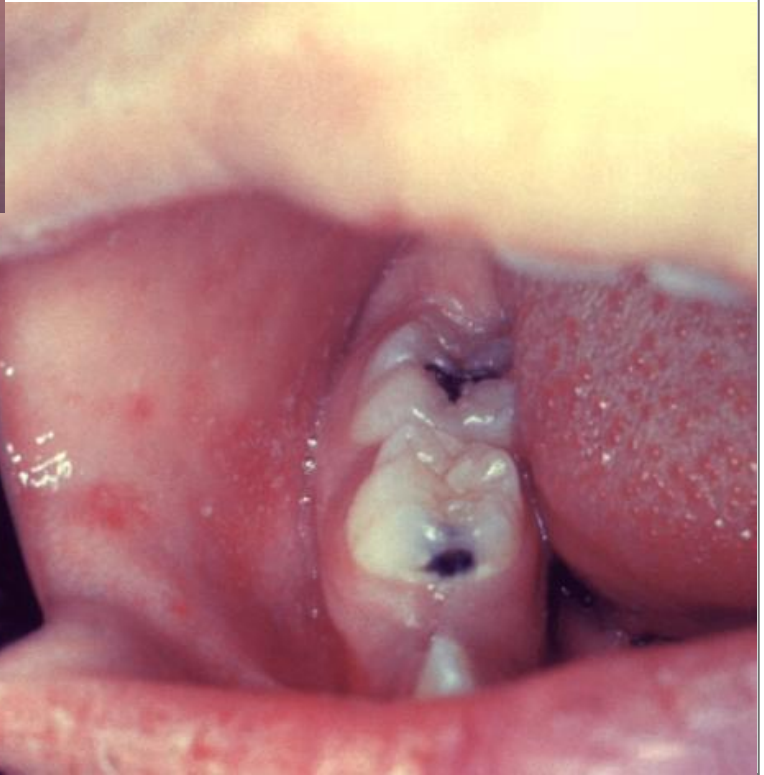
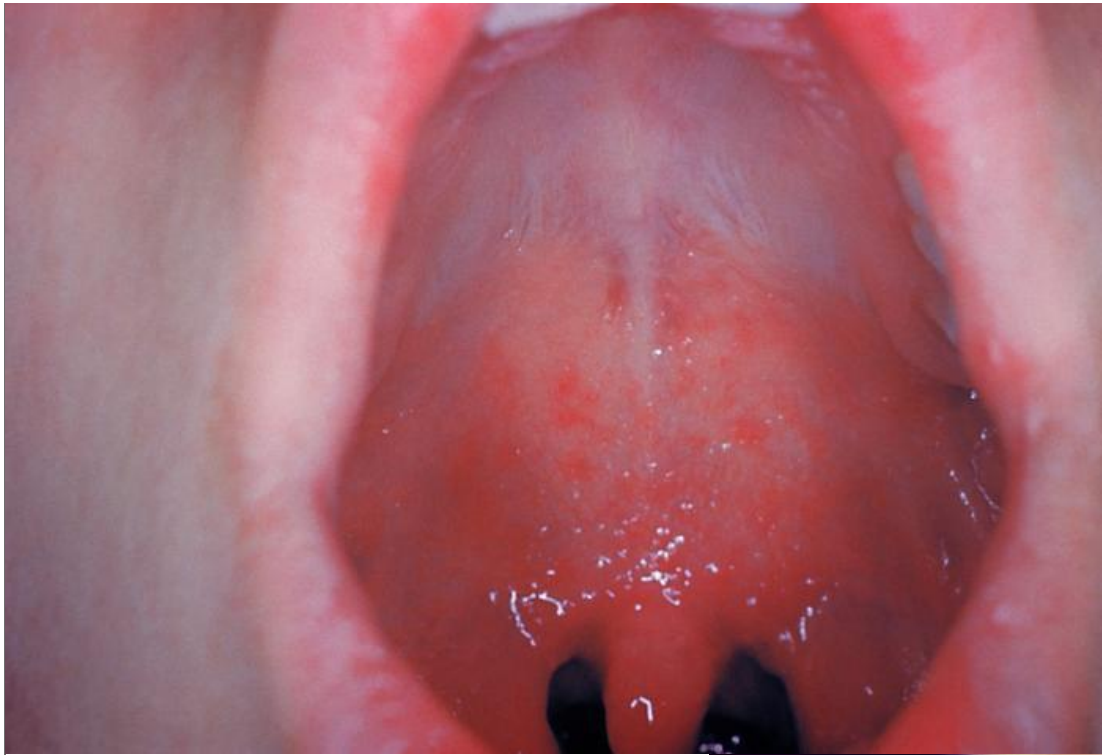
# Measles Vaccine Debates

“The outbreak of measles last year stoked **debate on vaccinations**. One study, *since debunked by dozens of further studies*, said childhood vaccines could be linked to higher rates of autism, and scores of parents have decided not to vaccinate their children.

Most medical officials have said the risk of complications from vaccines is so much lower than the risk of complications from illnesses, such as measles, that they recommend children get them. State laws enacted last year require vaccinations for children who go to public schools with very few exceptions.”

-ProMED, HealthMap, 5 APR 2016

A story published in the **Journal of the American Medical Association** [15 Mar 2016] said a review of 18 measles studies and 32 pertussis(whooping cough) studies found that children whose parents intentionally did not have them vaccinated contribute to disease outbreaks.



## Koplik Spots

[www.cdc.gov/measles](http://www.cdc.gov/measles)



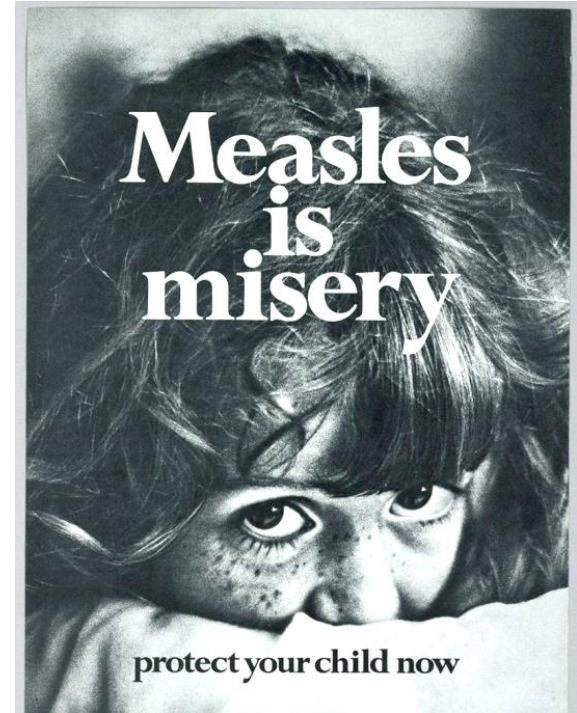
# Measles

- Vaccination

- US: first dose at 12 months
- Global: first dose at 9 months
- Booster at age 4-6 yrs

- Treatment

- Supportive care
- Monitor for bacterial superinfections
- Vitamin A once daily x 2 days



[all-that-is-interesting.com](http://all-that-is-interesting.com)

# Measles and Vitamin A

- Measles unmasks underlying vitamin A deficiency
- Vitamin A deficiency increases morbidity and mortality associated with measles

**Disaster/refugee settings are high risk for measles outbreaks – measles vaccine and vitamin A are essential tools in such settings**

# Measles Cases and Outbreaks

January 1 to February 20, 2015\*

# 154

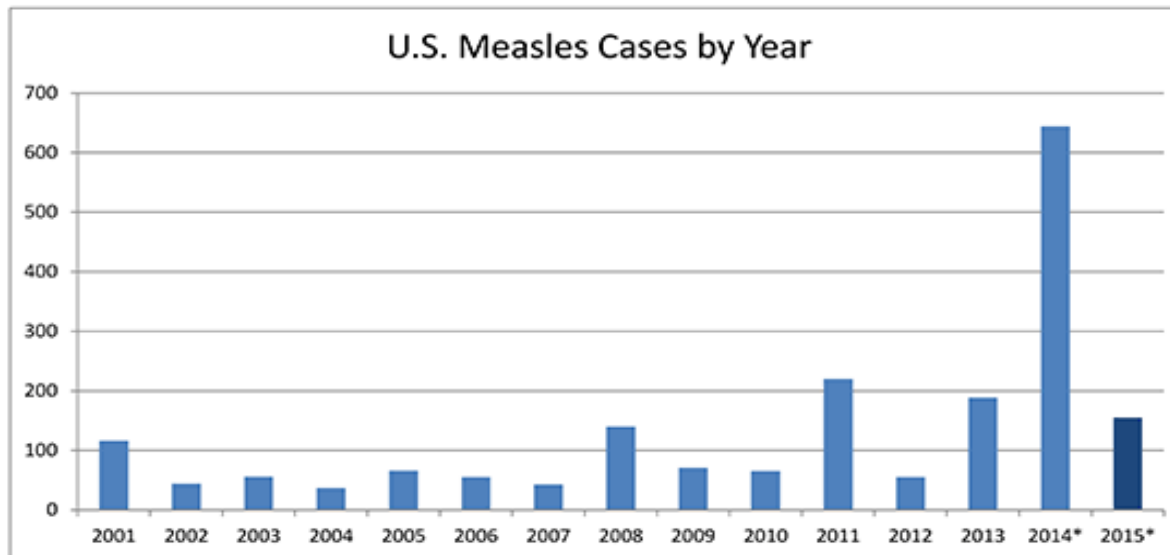
Cases

reported in 17 states and Washington DC: Arizona, California, Colorado, Delaware, Georgia, Illinois, Michigan, Minnesota, Nebraska, New Jersey, New York, Nevada, Pennsylvania, South Dakota, Texas, Utah, Washington

# 3

Outbreaks

representing 90% of reported cases this year



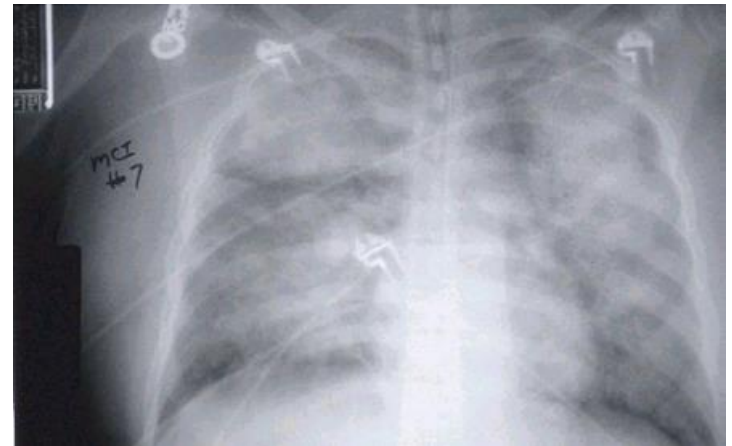
\*Provisional data reported to CDC's National Center for Immunization and Respiratory Diseases





# Hantavirus Pulmonary Syndrome

- New World Hantaviruses
  - ~300 cases per year, mortality up to 50%
  - Sporadic cases in the Americas: US, Canada, Argentina, Bolivia, Brazil, Chile, Panama, Paraguay, Uruguay
- Mice and rats are reservoirs
  - Urine, dropping, nesting materials are aerosolized and inhaled by humans
  - Bites and ingestion of contaminated food
  - Barns, outbuildings, and shed are exposure sites
- Incubation 1-4 weeks, initially non-specific myalgia, HA, chills, nausea, vomiting, GI symptoms
- Shortness of breath and cough develops later
  - Rapidly progressive cardiopulmonary phase
  - Bilateral infiltrates, pulmonary edema





Virus Research December 2011 (162)

# Nipah Virus

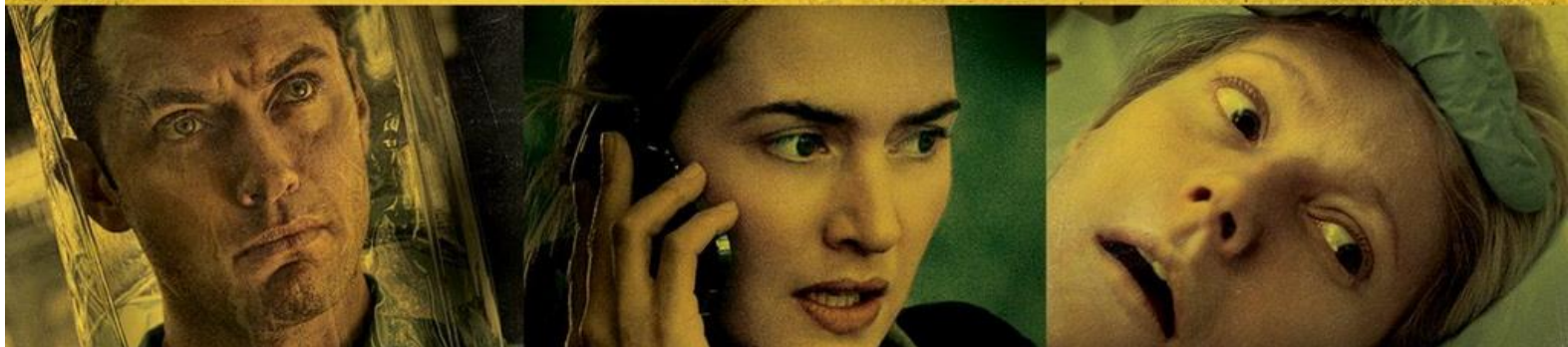
- RNA virus, Family: paramyxovirus
- Presents as a respiratory illness or meningoencephalitis, often leading to respiratory failure/coma/death
- Recent outbreaks in Malaysia and Bangladesh
- Reservoir: Fruit bats in Asia/Africa
- Infection occurs in humans, cats, dogs, pigs
- Humans often infected through direct contact with pigs; limited human-to-human transmission may be possible





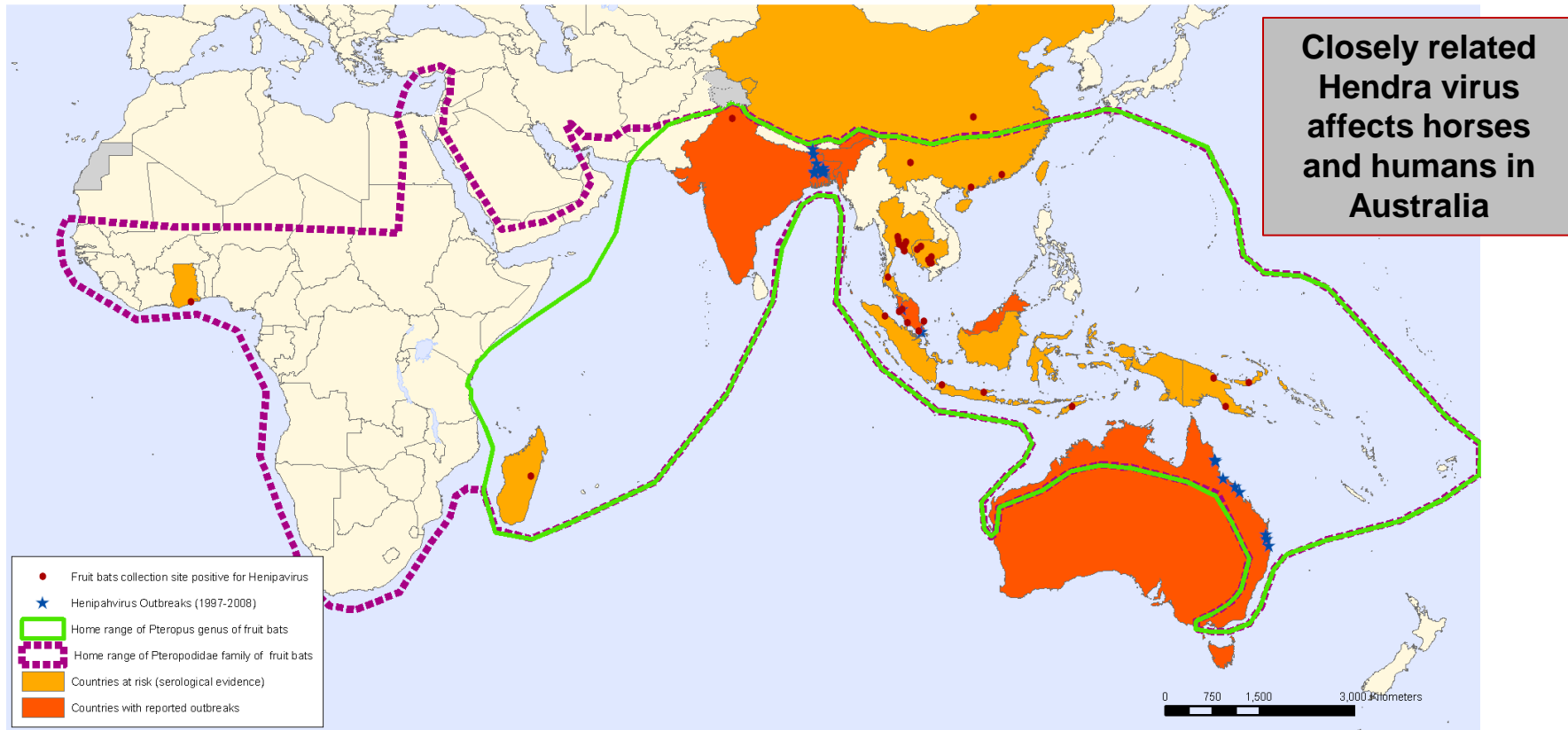
MARION  
COTILLARD    MATT  
DAMON    LAURENCE  
FISHBURNE    JUDE  
LAW    GWYNETH  
PALTROW    KATE  
WINSLET

**NOTHING SPREADS LIKE FEAR**  
**C O N T A G I O N**



# Nipah Virus

## Geographic distribution of Henipavirus outbreaks and fruit bats of Pteropodidae Family



The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement.

Data Source: Global Alert and Response Department  
World Health Organization  
Map Production: Public Health Information  
and Geographic Information Systems (GIS)  
World Health Organization



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# Bacterial Causes of Respiratory Disease

## Global Etiology:

*S. pneumoniae* (30-50%)

*H. influenzae* type B (10-30%)

*S. aureus*

*K. pneumoniae*



Still a very common cause of pneumonia wherever you are, in whatever population you're dealing with

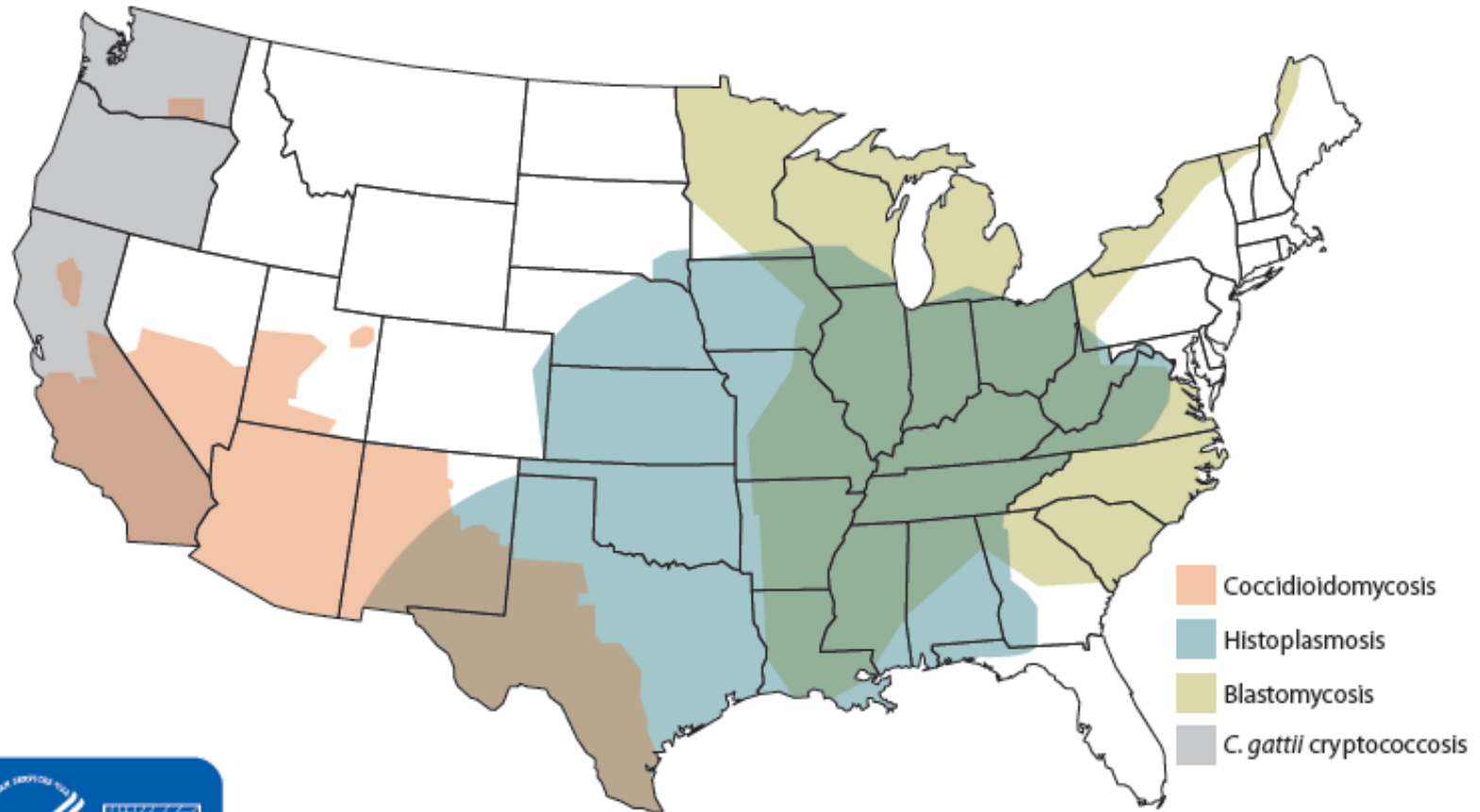
## Others to Consider:

Tuberculosis

Leptospirosis

Melioidosis

# Endemic Fungal Infections





# Endemic Fungal Infections



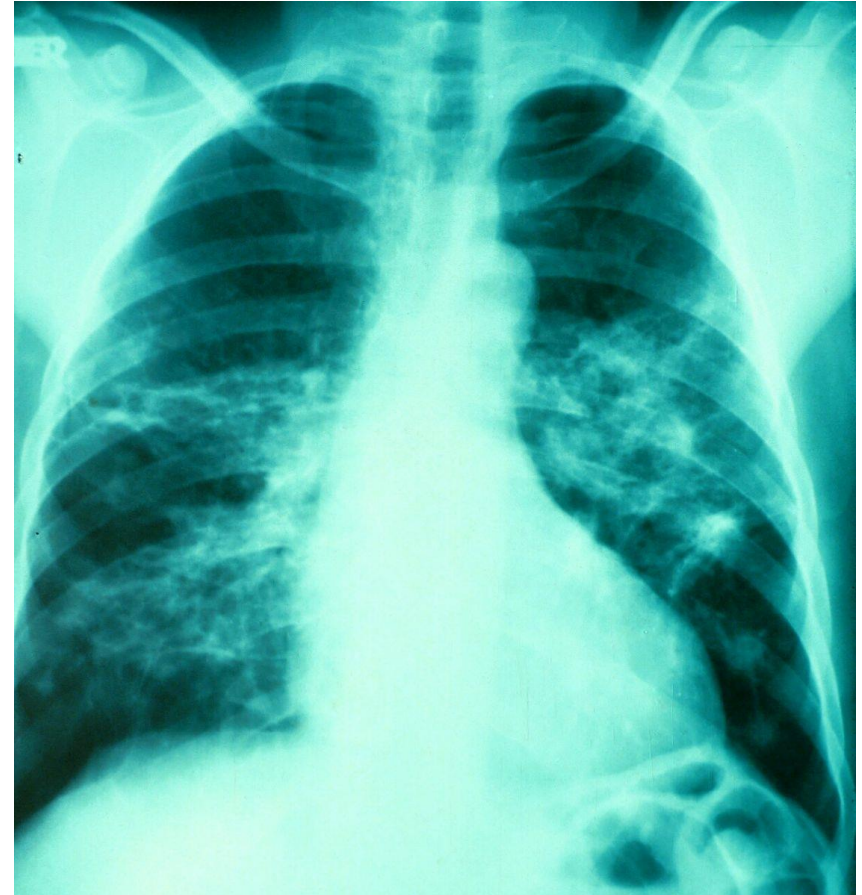
Geographic distribution of  
*Histoplasma capsulatum* (gray)  
and *Coccidioides immitis* (black) in  
the Americas

*Clin Infect Dis.* (2002) 35 (9): 1088-1095

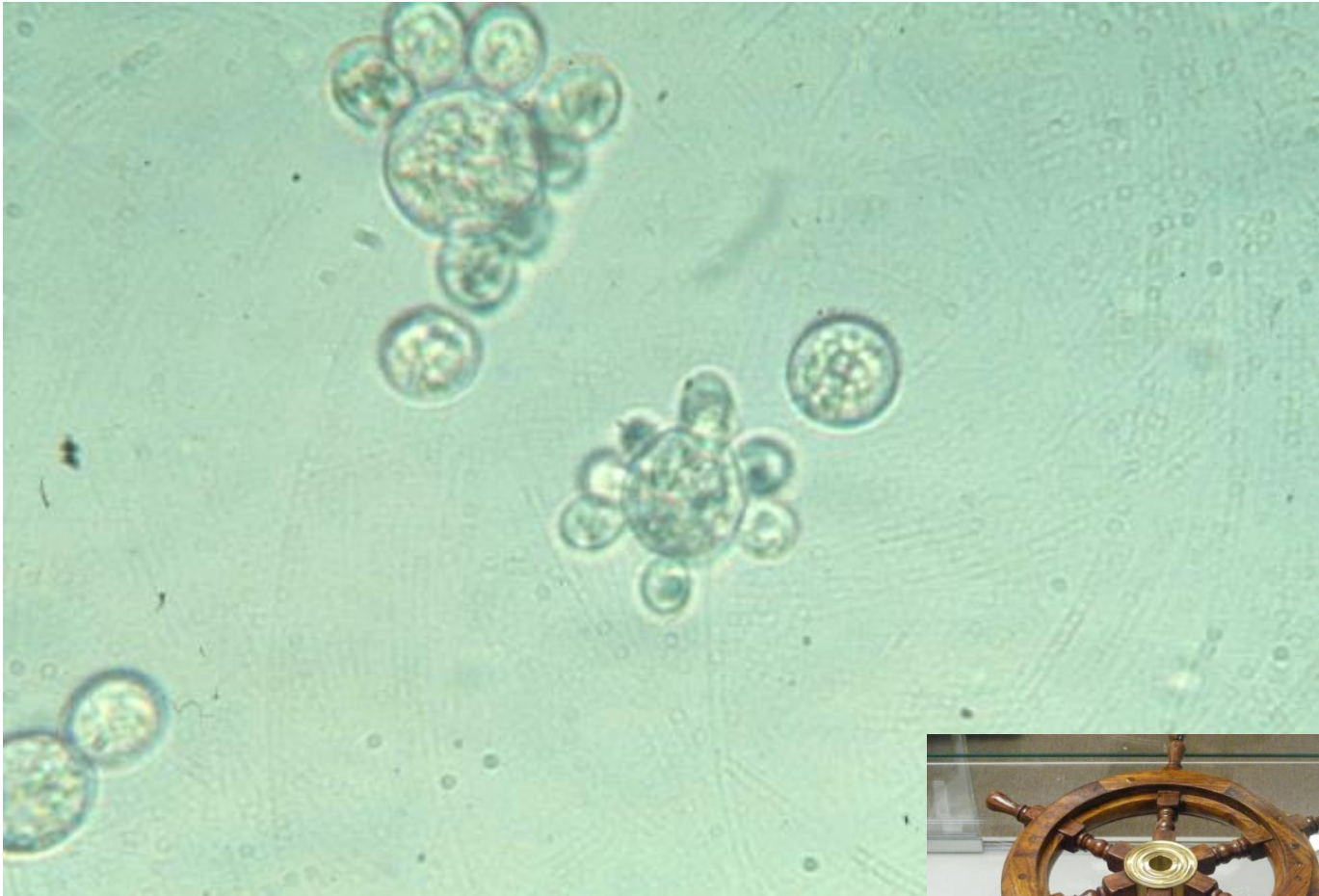
## **Case #2: HIV+ patient with shortness of breath**

- 35 year old HIV+ male presents with periodic fever, malaise, and weight loss for 3 months
- Has recently developed shortness of breath
- Spent most of his life in Brazil working in agriculture

# On Examination.....



# Wet mount of respiratory specimen



# Paracoccidioidomycosis

- Caused by the fungus *Paracoccidioides brasiliensis* or *Paracoccidioides lutzii*
- Classic appearance on microscopy: multiple budding yeasts (pilot's wheel)
- Causes a primary lung infection followed by secondary lesions in skin and mucous membranes



Manns BJ. *Clin Inf Dis*. 1996; 23: 1026-32.

# Paracoccidioidomycosis Geographic Distribution



# Paracoccidioidomycosis

## Clinical Presentations

### Acute Form

- Fever
- Weight loss
- Lymphadenopathy
- Hepatosplenomegaly
- Skin and mucosal lesions
- Absent lung findings

### Chronic Form

- Fever
- Weight loss
- Pulmonary infiltrates
- Cavitory lesions sometimes seen
- Skin and mucosal lesions



# What About Parasites?

# Case #3: Isn't this TB?

- 38 y/o male with right chest pain and dyspnea for one month
- Right spontaneous pneumothorax 12 months prior but otherwise healthy
- Pleural fluid analysis consistent with tuberculosis

# Chest X-Ray/CT



Song J, *Tuberc Respir Dis.* 2014; 76: 175-178.

# Case #3: Isn't this TB?

- Started on RIPE therapy for treatment of tuberculosis
- No improvement 3 weeks later

# Microscopic Analysis of Pleural Fluid



# And What Could This Be?





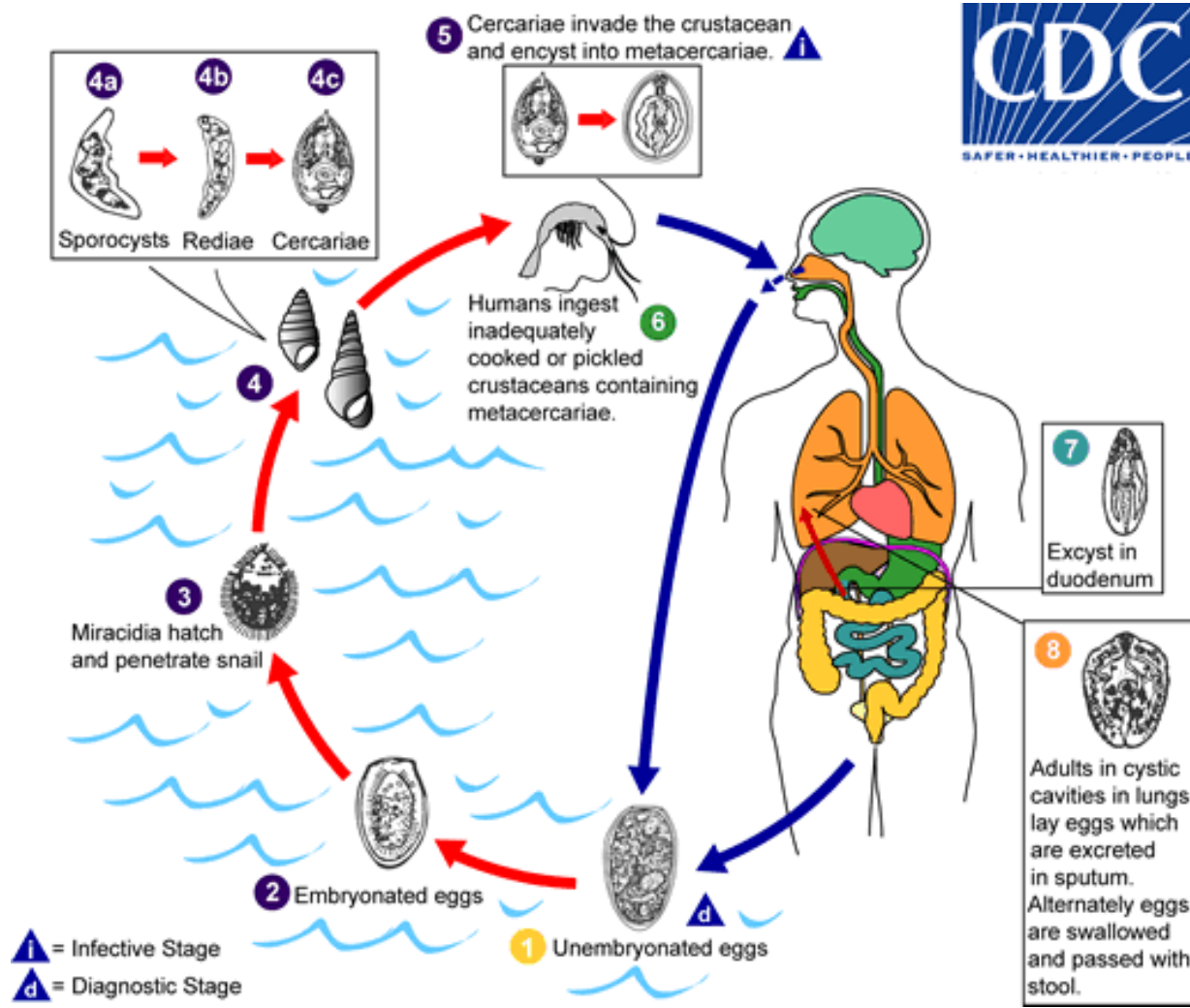
# Pleuropulmonary Paragonimiasis

- Infection by species of *Paragonimus* parasite
- Trematode – AKA the “lung fluke”
- Transmission to humans through ingestion of raw or undercooked crustaceans (crab, crayfish)



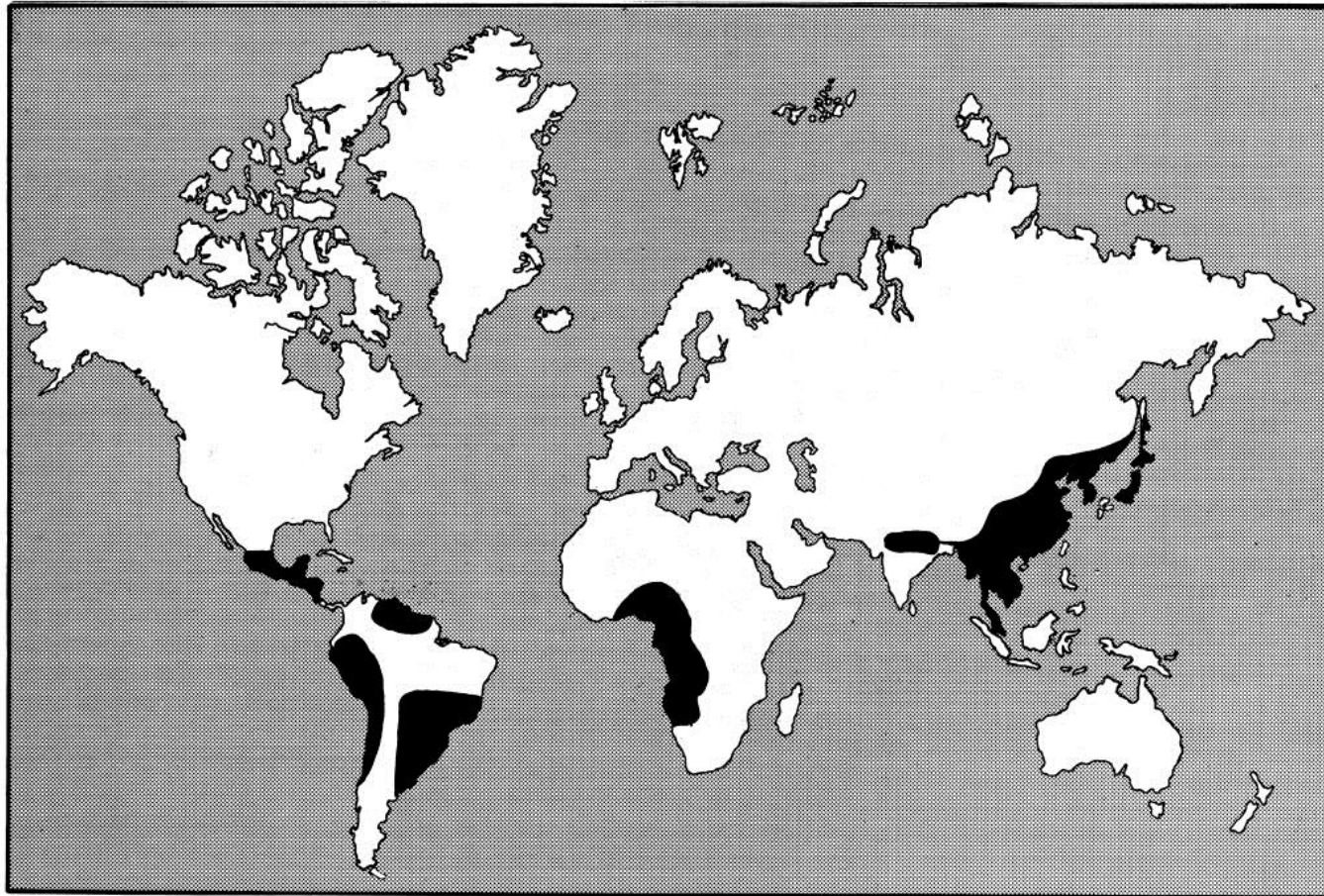
[www.cdc.gov/parasites/](http://www.cdc.gov/parasites/)  
[www.infectionlandscapes.org/2012/08/lung-flukes-paragonimiasis.html](http://www.infectionlandscapes.org/2012/08/lung-flukes-paragonimiasis.html)

# Paragonimus Life Cycle



<http://www.cdc.gov/dpdx/paragonimiasis/index.html>

# Geographic Distribution of Paragonimiasis



[www.infectionlandscapes.org/2012/08/lung-flukes-paragonimiasis.html](http://www.infectionlandscapes.org/2012/08/lung-flukes-paragonimiasis.html)

# Paragonimiasis

## Clinical Presentation

- Acute illness
  - Cough, abdominal pain, chest pain, low-grade fever, SOB
  - May be mild illness or asymptomatic
- Chronic infection
  - Productive cough, brown-colored or blood-tinged sputum
  - Persistence of low grade infection for 20+ years
- Complications
  - Cavitory lung disease
  - Pleural effusion
  - CNS infection – parenchymal lesions or meningitis
  - Can infect other tissues – muscle, heart, liver, spleen



# Benefits of Accurate Diagnosis

- Acute illness
  - Cough, abdominal pain, chest pain, low-grade fever, SOB
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- Complications
  - Cavitory lung disease
  - Pleural effusion
  - CNS infection – parenchymal lesions or meningitis
  - Can infect other tissues – muscle, heart, liver, spleen

# Benefits of Accurate Diagnosis

- Treatment for pleural tuberculosis:
  - Several months of multi-drug therapy
- Treatment for pleural paragonimiasis:
  - Praziquantal x 2d
  - Alternative: Triclabendazole x 1-2 days

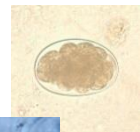
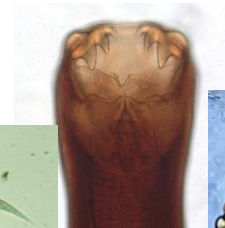


# Lung Effects from other 'Worm' Infections: Loeffler's Syndrome and Tropical Pulmonary Eosinophilia

- Cough, dyspnea
- Paroxysmal nocturnal asthma (TPE)
- Pulmonary infiltrates
- Peripheral eosinophilia
- Caused by immune response to GI or bloodstream helminths

## GI Helminths → Loeffler's Syndrome

*Ascaris*, Hookworm, Strongyloides



## Microfilarial Infections → TPE

Lymphatic filariasis (*W. bancrofti*, *B. malayi*)



# **Respiratory Signs/Symptoms in Other Tropical Infections**

**Case # 4: During a deployment to Nigeria, an otherwise healthy 23 y/o active duty male presents with fever, back pain, and a cough.**

**What would you include in your differential diagnosis?**

# Respiratory Signs/Symptoms in Other Tropical Infections

1. Malaria!
2. Malaria!
3. Malaria!
4. Everything else

In a patient presenting with fever with h/o exposure in a malaria endemic area, ALWAYS consider malaria until ruled out!

# Questions?